

L Number	Hits	Search Text	DB	Time stamp
1	0	walterova?	USPAT; EPO; JPO; DERWENT	2001/11/02 14:27
2	0	walterova.in	USPAT; EPO; JPO; DERWENT	2001/11/02 14:27
3	0	walterova\$.in	USPAT; EPO; JPO; DERWENT	2001/11/02 14:27
4	2	walterova\$.in.	USPAT; EPO; JPO; DERWENT	2001/11/02 14:28
5	679	alkaloid same (isolat\$4 or purif\$ or extrac\$) same (plant or herb or papaveraceae or cactacea or leguminoseae or fumariaceae)	USPAT; EPO; JPO; DERWENT	2001/11/02 14:31
6	85	(alkaloid same (isolat\$4 or purif\$ or extrac\$) same (plant or herb or papaveraceae or cactacea or leguminoseae or fumariaceae)) same (chromat\$ or column or hplc or waters!)	USPAT; EPO; JPO; DERWENT	2001/11/02 14:36
7	5	((alkaloid same (isolat\$4 or purif\$ or extrac\$) same (plant or herb or papaveraceae or cactacea or leguminoseae or fumariaceae)) same (chromat\$ or column or hplc or waters!)) same (neutral\$7)	USPAT; EPO; JPO; DERWENT	2001/11/02 14:47
8	0	huperzine same isoquinoline	USPAT; EPO; JPO; DERWENT	2001/11/02 14:47
9	4	huperzine and isoquinoline	USPAT; EPO; JPO; DERWENT	2001/11/02 14:47

\$%^STN;HighlightOn= ***;HighlightOff=*** ;
Trying 3106016892...Open

Welcome to STN International! Enter x:x
LOGINID:sssptal65lpxp
PASSWORD:
TERMINAL (ENTER 1, 2, 3, OR ?):2

* * * * * Welcome to STN International * * * * *

NEWS	1		Web Page URLs for STN Seminar Schedule - N. America
NEWS	2	Dec 17	The CA Lexicon available in the CAPLUS and CA files
NEWS	3	Feb 06	Engineering Information Encompass files have new names
NEWS	4	Feb 16	TOXLINE no longer being updated
NEWS	5	Apr 23	Search Derwent WPINDEX by chemical structure
NEWS	6	Apr 23	PRE-1967 REFERENCES NOW SEARCHABLE IN CAPLUS AND CA
NEWS	7	May 07	DGENE Reload
NEWS	8	Jun 20	Published patent applications (A1) are now in USPATFULL
NEWS	9	JUL 13	New SDI alert frequency now available in Derwent's DWPI and DPCI
NEWS	10	Aug 23	In-process records and more frequent updates now in MEDLINE
NEWS	11	Aug 23	PAGE IMAGES FOR 1947-1966 RECORDS IN CAPLUS AND CA
NEWS	12	Aug 23	Adis Newsletters (ADISNEWS) now available on STN
NEWS	13	Sep 17	IMSworld Pharmaceutical Company Directory name change to PHARMASEARCH
NEWS	14	Oct 09	Korean abstracts now included in Derwent World Patents Index
NEWS	15	Oct 09	Number of Derwent World Patents Index updates increased
NEWS	16	Oct 15	Calculated properties now in the REGISTRY/ZREGISTRY File
NEWS	17	Oct 22	Over 1 million reactions added to CASREACT
NEWS	18	Oct 22	DGENE GETSIM has been improved
NEWS	19	Oct 29	AAASD no longer available
NEWS EXPRESS			August 15 CURRENT WINDOWS VERSION IS V6.0c, CURRENT MACINTOSH VERSION IS V6.0 (ENG) AND V6.0J (JP), AND CURRENT DISCOVER FILE IS DATED 07 AUGUST 2001
NEWS HOURS			STN Operating Hours Plus Help Desk Availability
NEWS INTER			General Internet Information
NEWS LOGIN			Welcome Banner and News Items
NEWS PHONE			Direct Dial and Telecommunication Network Access to STN
NEWS WWW			CAS World Wide Web Site (general information)

Enter NEWS followed by the item number or name to see news on that
specific topic.

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* * * * * STN Columbus * * * * *

FILE 'HOME' ENTERED AT 11:15:07 ON 02 NOV 2001

=> index bioscience napralert

FILE 'DRUGMONOG' ACCESS NOT AUTHORIZED
COST IN U.S. DOLLARS

	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	0.60	0.60

INDEX 'ADISALERTS, ADISINSIGHT, ADISNEWS, AGRICOLA, ANABSTR, AQUASCI,
BIOBUSINESS, BIOCOMMERCE, BIOSIS, BIOTECHABS, BIOTECHDS, BIOTECHNO, CABA,
CANCERLIT, CAPLUS, CEABA-VTB, CEN, CIN, CONFSCI, CROPB, CROPU, DDFB,
DDFU, DGENE, DRUGB, DRUGLAUNCH, DRUGMONOG2, ...'
ENTERED AT 11:17:07 ON 02 NOV 2001

60 FILES IN THE FILE LIST IN STNINDEX

Enter SET DETAIL ON to see search term postings or to view
search error messages that display as 0* with SET DETAIL OFF.

=> s morphine(1) poppy (1) (extract? or isolat? or purif?)

7	FILE AGRICOLA
13	FILE ANABSTR
1	FILE BIOBUSINESS
35	FILE BIOSIS
14	FILE BIOTECHABS
14	FILE BIOTECHDS
9	FILE BIOTECHNO
12 FILES SEARCHED...	
19	FILE CABA
93	FILE CAPLUS
10	FILE CIN
4	FILE DDFU
23 FILES SEARCHED...	
25	FILE DGENE
9	FILE DRUGU
24	FILE EMBASE
7	FILE ESBIODBASE
34 FILES SEARCHED...	
1	FILE HEALSAFE
3	FILE IFIPAT
3	FILE JICST-EPLUS
7	FILE LIFESCI
25	FILE MEDLINE
46 FILES SEARCHED...	
2	FILE NTIS
4	FILE PASCAL
19	FILE PHIN
16	FILE PROMT
16	FILE SCISEARCH
17	FILE TOXLIT
29	FILE USPATFULL
14	FILE WPIDS
58 FILES SEARCHED...	
14	FILE WPINDEX

7 FILE NAPRALERT

30 FILES HAVE ONE OR MORE ANSWERS, 60 FILES SEARCHED IN STNINDEX

L1 QUE MORPHINE(L) POPPY (L) (EXTRACT? OR ISOLAT? OR PURIF?)

=> s 11 and (method? or proce? or protocol?)

```
1 FILE AGRICOLA
8 FILE ANABSTR
1 FILE BIOBUSINESS
18 FILE BIOSIS
9 FILES SEARCHED...
3 FILE BIOTECHABS
3 FILE BIOTECHDS
3 FILE BIOTECHNO
9 FILE CABA
46 FILE CAPLUS
15 FILES SEARCHED...
1 FILE CIN
3 FILE DDFU
10 FILE DGENE
24 FILES SEARCHED...
6 FILE DRUGU
14 FILE EMBASE
2 FILE ESBIODASE
33 FILES SEARCHED...
3 FILE IFIPAT
40 FILES SEARCHED...
3 FILE JICST-EPLUS
2 FILE LIFESCI
10 FILE MEDLINE
2 FILE NTIS
47 FILES SEARCHED...
3 FILE PASCAL
49 FILES SEARCHED...
1 FILE PHIN
9 FILE PROMT
3 FILE SCISEARCH
7 FILE TOXLIT
29 FILE USPATFULL
57 FILES SEARCHED...
9 FILE WPIDS
9 FILE WPINDEX
59 FILES SEARCHED...
4 FILE NAPRALERT
```

29 FILES HAVE ONE OR MORE ANSWERS, 60 FILES SEARCHED IN STNINDEX

L2 QUE L1 AND (METHOD? OR PROCE? OR PROTOCOL?)

=> 2 and vat extract?

<-----User Break----->

u

=> s 12 and vat extract?

```
9 FILES SEARCHED...
```

14 FILES SEARCHED...
23 FILES SEARCHED...
33 FILES SEARCHED...
<-----User Break----->
u
=> s ll and vat extract?

14 FILES SEARCHED...
<-----User Break----->
u

=> s isoquinoline alkaloid or codeine or curare or heroin or morphine or
papaverine or tubocurarine or benzyloisoquinoline alkaloid?

4072	FILE ADISALERTS
173	FILE ADISINSIGHT
850	FILE ADISNEWS
561	FILE AGRICOLA
1368	FILE ANABSTR
171	FILE AQUASCI
743	FILE BIOBUSINESS
55	FILE BIOCOMMERCE
57504	FILE BIOSIS
238	FILE BIOTECHABS
238	FILE BIOTECHDS
3295	FILE BIOTECHNO
1764	FILE CABA
3086	FILE CANCERLIT
47508	FILE CAPLUS
52	FILE CEABA-VTB
47	FILE CEN
648	FILE CIN
1926	FILE CONFSCI
20	FILE CROPB
32	FILE CROPU
21	FILES SEARCHED...
20623	FILE DDFB
29875	FILE DDFU
1843	FILE DGENE
20623	FILE DRUGB
978	FILE DRUGLAUNCH
4719	FILE DRUGMONOG2
104	FILE DRUGNL
31743	FILE DRUGU
119	FILE DRUGUPDATES
273	FILE EMBAL
73230	FILE EMBASE
6227	FILE ESBIODBASE
21	FILE FROSTI
22	FILE FSTA
115	FILE GENBANK
248	FILE HEALSAFE
39	FILES SEARCHED...
781	FILE IFIPAT
3680	FILE JICST-EPLUS
7	FILE KOSMET
8111	FILE LIFESCI
16	FILE MEDICONF

53931 FILE MEDLINE
437 FILE NIOSHTIC
617 FILE NTIS
26 FILE OCEAN
15458 FILE PASCAL
247 FILE PHAR
12 FILE PHIC
1316 FILE PHIN
3512 FILE PROMT
35286 FILE SCISEARCH
54 FILES SEARCHED...
3 FILE SYNTHLINE
30119 FILE TOXLIT
7020 FILE USPATFULL
2471 FILE WPIDS
2471 FILE WPINDEX
8862 FILE NAPRALERT

58 FILES HAVE ONE OR MORE ANSWERS, 60 FILES SEARCHED IN STNINDEX

L3 QUE ISOQUINOLINE ALKALOID OR CODEINE OR CURARE OR HEROIN OR MORPHINE OR PA
PAVERINE OR TUBOCURARINE OR BENZYLISOQUINOLINE ALKALOID?

=> s 13 (1) (extract? or purif? or isolat?)

80 FILE ADISALERTS
19 FILE ADISINSIGHT
19 FILE ADISNEWS
68 FILE AGRICOLA
431 FILE ANABSTR
41 FILE AQUASCI
73 FILE BIOBUSINESS
1 FILE BIOCOMMERCE
3449 FILE BIOSIS
123 FILE BIOTECHABS
123 FILE BIOTECHDS
442 FILE BIOTECHNO
12 FILES SEARCHED...
337 FILE CABA
107 FILE CANCERLIT
5065 FILE CAPLUS
10 FILE CEABA-VTB
16 FILE CEN
48 FILE CIN
38 FILE CONFSCI
5 FILE CROPU
302 FILE DDFB
1570 FILE DDFU
176 FILE DGENE
302 FILE DRUGB
26 FILE DRUGLAUNCH
385 FILE DRUGMONOG2
27 FILES SEARCHED...
1 FILE DRUGNL
2888 FILE DRUGU
12 FILE DRUGUPDATES
20 FILE EMBAL

3354 FILE EMBASE
684 FILE ESBIODBASE
2 FILE FROSTI
5 FILE FSTA
10 FILE GENBANK
8 FILE HEALSAFE
66 FILE IFIPAT

40 FILES SEARCHED...

198 FILE JICST-EPLUS
674 FILE LIFESCI
3188 FILE MEDLINE
56 FILE NIOSHTIC
49 FILE NTIS
7 FILE OCEAN
873 FILE PASCAL
22 FILE PHAR
111 FILE PHIN
194 FILE PROMT
1700 FILE SCISEARCH

54 FILES SEARCHED...

1 FILE SYNTHLINE
2965 FILE TOXLIT
4516 FILE USPATFULL
241 FILE WPIDS
241 FILE WPINDEX
4938 FILE NAPRALERT

54 FILES HAVE ONE OR MORE ANSWERS, 60 FILES SEARCHED IN STNINDEX

L4 QUE L3 (L) (EXTRACT? OR PURIF? OR ISOLAT?)

=> s l4 and vat extract?

<-----User Break----->

u

=> s l4 and vat

13 FILES SEARCHED...

23 FILES SEARCHED...

37 FILES SEARCHED...

49 FILES SEARCHED...

1 FILE SCISEARCH
18 FILE USPATFULL
1 FILE WPIDS

58 FILES SEARCHED...

1 FILE WPINDEX

4 FILES HAVE ONE OR MORE ANSWERS, 60 FILES SEARCHED IN STNINDEX

L5 QUE L4 AND VAT

=> d rank

F1 18 USPATFULL
F2 1 SCISEARCH
F3 1 WPIDS
F4 1 WPINDEX

=> fil f2

COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	14.85	15.45

FILE 'SCISEARCH' ENTERED AT 11:36:54 ON 02 NOV 2001
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FILE COVERS 1974 TO 26 Oct 2001 (20011026/ED)

=> s 15

2535 ISOQUINOLINE
9643 ALKALOID
117 ISOQUINOLINE ALKALOID
(ISOQUINOLINE(W)ALKALOID)
2000 CODEINE
457 CURARE
4229 HEROIN
26191 MORPHINE
2433 PAPAVERINE
1478 TUBOCURARINE
196 BENZYLISOQUINOLINE
25042 ALKALOID?
128 BENZYLISOQUINOLINE ALKALOID?
(BENZYLISOQUINOLINE(W)ALKALOID?)
257688 EXTRACT?
200469 PURIF?
488986 ISOLAT?
1700 L3 (L) (EXTRACT? OR PURIF? OR ISOLAT?)
811 VAT
L6 1 L4 AND VAT

=> d 16 1- all

YOU HAVE REQUESTED DATA FROM 1 ANSWERS - CONTINUE? Y/(N):y

L6 ANSWER 1 OF 1 SCISEARCH COPYRIGHT 2001 ISI (R)
AN 95:779834 SCISEARCH
GA The Genuine Article (R) Number: TD066
TI MORPHINE-INDUCED ALTERATIONS ON DNA-BINDING PROTEINS IN DEVELOPING
RAT-BRAIN
AU TENCHEVA Z (Reprint); VELICHKOVA A; ANGELOVA A
CS BULGARIAN ACAD SCI, BRAIN RES INST, ACAD G BONCHEV B123, BU-1113 SOFIA,
BULGARIA (Reprint); UNIV SOFIA, DEPT BIOCHEM, SOFIA, BULGARIA
CYA BULGARIA
SO METHODS AND FINDINGS IN EXPERIMENTAL AND CLINICAL PHARMACOLOGY, (SEP 1995)
Vol. 17, No. 7, pp. 449-454.
ISSN: 0379-0355.
DT Article; Journal
FS LIFE
LA ENGLISH
REC Reference Count: 22
AB Endogenous opioids and opiate drugs inhibit nervous system maturation

through both direct and indirect mechanisms. Recently much attention has been directed toward changes in the postreceptor events and it has been speculated that the regulation of gene expression may be involved in the development of drug tolerance and dependence. We investigated the changes in the levels of in vitro RNA synthesis in developing rat brain after continuous block of opioid receptors. Repeated naloxone treatment induced increased levels (27-48%) of RNA synthesis during the early postnatal period. Using mobility gel shift assay the presence of octamer binding proteins (Oct-1) and the replication differentiation transcription factor CTF/NF1 in the developing ***vat*** brain were studied both after single or repeated ***morphine*** and naloxone treatment. Decreased Oct-1 binding activity in brain protein ***extracts*** 1 h after ***morphine*** application was registered, while opioid antagonist naloxone exerted an opposite effect on this octamer protein following single drug treatment. Repeated administration of ***morphine*** or naloxone decreased markedly the DNA-binding affinity of Oct-1. The binding activity of CTF/NF1 changes differently showed higher levels assessed 30-120 min after ***morphine*** administration. The opposite trend of the changes in opiate drug and opioid antagonist animals suggests opioid receptor-mediated regulation of Oct-1 and CTF/NF1 transcription factors.

CC PHARMACOLOGY & PHARMACY

ST Author Keywords: MORPHINE; NALOXONE; DNA BINDING PROTEINS; OCT-1; CTF/NF1; TRANSCRIPTIONAL REGULATION; TRANSCRIPTION FACTORS; DEVELOPING BRAIN

STP KeyWords Plus (R): CELL-PROLIFERATION; MAMMALIAN-CELLS; TRANSCRIPTION; REPLICATION; ANTAGONIST; NALTREXONE; EXPOSURE; NALOXONE; REGIONS

RF 93-3472 002; RNA POLYMERASE-II TRANSCRIPTION; TATA-BINDING PROTEIN; ACTIVATION DOMAINS; FUNCTIONAL PREINITIATION COMPLEX
93-6382 001; PIT-1/GHF-1 TRANSCRIPTION FACTOR EXPRESSION; POU DOMAIN PROTEIN; RAT THYROTROPIN-BETA GENE

RE

Referenced Author (RAU)	Year (RPY)	VOL (RVL)	PG (RPG)	Referenced Work (RWK)
ANDREWS N C	1991	19	2499	NUCLEIC ACIDS RES
BARDO M T	1983	22	453	NEUROPHARMACOLOGY
CHANG S L	1993	4	25	MOL CELL NEUROSCI
COYLE J T	1976	15	555	NEUROPHARMACOLOGY
HADJIOLOV A A	1965	26	383	J CELL BIOL
HAUSER K F	1993		23	NEUROBIOLOGY OPIATES
HE X	1989	340	35	NATURE
JOHNSON P F	1989	58	799	ANNU REV BIOCHEM
KORNBLUM H I	1987	31	45	DEV BRAIN RES
LORBER B A	1990	531	329	BRAIN RES
MASEDA C	1983	14	S 237	NEUROSCI LETT S
MITCHELL P J	1989	245	371	SCIENCE
OSUGI T	1994	21	256	MOL BRAIN RES
SANTORO C	1988	334	218	NATURE
SCHMAHL W	1989	486	297	BRAIN RES
SCHREIBER E	1989		33	TISSUE SPECIFIC GENE
SOLLNERWEBB B	1975	14	2915	BIOCHEMISTRY-US
TSANG D	1980	188	199	BRAIN RES
TSANG D	1982	3	637	DEV BRAIN RES

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=>

=> d his

(FILE 'HOME' ENTERED AT 11:15:07 ON 02 NOV 2001)

INDEX 'ADISALERTS, ADISINSIGHT, ADISNEWS, AGRICOLA, ANABSTR, AQUASCI, BIOBUSINESS, BIOCOMMERCE, BIOSIS, BIOTECHABS, BIOTECHDS, BIOTECHNO, CABA, CANCERLIT, CAPLUS, CEABA-VTB, CEN, CIN, CONFSCI, CROPB, CROPU, DDFB, DDFU, DGENE, DRUGB, DRUGLAUNCH, DRUGMONOG2, ...' ENTERED AT 11:17:07 ON 02 NOV 2001

SEA MORPHINE(L) POPPY (L) (EXTRACT? OR ISOLAT? OR PURIF?)

7 FILE AGRICOLA
13 FILE ANABSTR
1 FILE BIOBUSINESS
35 FILE BIOSIS
14 FILE BIOTECHABS
14 FILE BIOTECHDS
9 FILE BIOTECHNO
19 FILE CABA
93 FILE CAPLUS
10 FILE CIN
4 FILE DDFU
25 FILE DGENE
9 FILE DRUGU
24 FILE EMBASE
7 FILE ESBIODBASE
1 FILE HEALSAFE
3 FILE IFIPAT
3 FILE JICST-EPLUS
7 FILE LIFESCI
25 FILE MEDLINE
2 FILE NTIS
4 FILE PASCAL
19 FILE PHIN
16 FILE PROMT
16 FILE SCISEARCH
17 FILE TOXLIT
29 FILE USPATFULL
14 FILE WPIDS
14 FILE WPINDEX
7 FILE NAPRALERT

L1 QUE MORPHINE(L) POPPY (L) (EXTRACT? OR ISOLAT? OR PURIF?)

SEA L1 AND (METHOD? OR PROCE? OR PROTOCOL?)

1 FILE AGRICOLA
8 FILE ANABSTR
1 FILE BIOBUSINESS
18 FILE BIOSIS
3 FILE BIOTECHABS
3 FILE BIOTECHDS
3 FILE BIOTECHNO
9 FILE CABA
46 FILE CAPLUS
1 FILE CIN
3 FILE DDFU
10 FILE DGENE
6 FILE DRUGU

14 FILE EMBASE
2 FILE ESBIODBASE
3 FILE IFIPAT
3 FILE JICST-EPLUS
2 FILE LIFESCI
10 FILE MEDLINE
2 FILE NTIS
3 FILE PASCAL
1 FILE PHIN
9 FILE PROMT
3 FILE SCISEARCH
7 FILE TOXLIT
29 FILE USPATFULL
9 FILE WPIDS
9 FILE WPINDEX
4 FILE NAPRALERT
L2 QUE L1 AND (METHOD? OR PROCE? OR PROTOCOL?)

SEA 2 AND VAT EXTRACT?

SEA L2 AND VAT EXTRACT?

SEA L1 AND VAT EXTRACT?

SEA ISOQUINOLINE ALKALOID OR CODEINE OR CURARE OR HEROIN OR MOR

4072 FILE ADISALERTS
173 FILE ADISINSIGHT
850 FILE ADISNEWS
561 FILE AGRICOLA
1368 FILE ANABSTR
171 FILE AQUASCI
743 FILE BIOBUSINESS
55 FILE BIOCOMMERCE
57504 FILE BIOSIS
238 FILE BIOTECHABS
238 FILE BIOTECHDS
3295 FILE BIOTECHNO
1764 FILE CABA
3086 FILE CANCERLIT
47508 FILE CAPLUS
52 FILE CEABA-VTB
47 FILE CEN
648 FILE CIN
1926 FILE CONFSCI
20 FILE CROPB
32 FILE CROPU
20623 FILE DDFB
29875 FILE DDFU
1843 FILE DGENE
20623 FILE DRUGB
978 FILE DRUGLAUNCH
4719 FILE DRUGMONOG2
104 FILE DRUGNL
31743 FILE DRUGU
119 FILE DRUGUPDATES
273 FILE EMBAL

73230 FILE EMBASE
 6227 FILE ESBIODBASE
 21 FILE FROSTI
 22 FILE FSTA
 115 FILE GENBANK
 248 FILE HEALSAFE
 781 FILE IFIPAT
 3680 FILE JICST-EPLUS
 7 FILE KOSMET
 8111 FILE LIFESCI
 16 FILE MEDICONF
 53931 FILE MEDLINE
 437 FILE NIOSHTIC
 617 FILE NTIS
 26 FILE OCEAN
 15458 FILE PASCAL
 247 FILE PHAR
 12 FILE PHIC
 1316 FILE PHIN
 3512 FILE PROMT
 35286 FILE SCISEARCH
 3 FILE SYNTHLINE
 30119 FILE TOXLIT
 7020 FILE USPATFULL
 2471 FILE WPIDS
 2471 FILE WPINDEX
 8862 FILE NAPRALERT

L3

QUE ISOQUINOLINE ALKALOID OR CODEINE OR CURARE OR HEROIN OR MOR

 SEA L3 (L) (EXTRACT? OR PURIF? OR ISOLAT?)

80 FILE ADISALERTS
 19 FILE ADISINSIGHT
 19 FILE ADISNEWS
 68 FILE AGRICOLA
 431 FILE ANABSTR
 41 FILE AQUASCI
 73 FILE BIOBUSINESS
 1 FILE BIOCOMMERCE
 3449 FILE BIOSIS
 123 FILE BIOTECHABS
 123 FILE BIOTECHDS
 442 FILE BIOTECHNO
 337 FILE CABA
 107 FILE CANCERLIT
 5065 FILE CAPLUS
 10 FILE CEABA-VTB
 16 FILE CEN
 48 FILE CIN
 38 FILE CONFSCI
 5 FILE CROPU
 302 FILE DDFB
 1570 FILE DDFU
 176 FILE DGENE
 302 FILE DRUGB
 26 FILE DRUGLAUNCH
 385 FILE DRUGMONOG2

```

1 FILE DRUGNL
2888 FILE DRUGU
12 FILE DRUGUPDATES
20 FILE EMBAL
3354 FILE EMBASE
684 FILE ESBIODBASE
2 FILE FROSTI
5 FILE FSTA
10 FILE GENBANK
8 FILE HEALSAFE
66 FILE IFIPAT
198 FILE JICST-EPLUS
674 FILE LIFESCI
3188 FILE MEDLINE
56 FILE NIOSHTIC
49 FILE NTIS
7 FILE OCEAN
873 FILE PASCAL
22 FILE PHAR
111 FILE PHIN
194 FILE PROMT
1700 FILE SCISEARCH
1 FILE SYNTHLINE
2965 FILE TOXLIT
4516 FILE USPATFULL
241 FILE WPIDS
241 FILE WPINDEX
4938 FILE NAPRALERT

```

L4 QUE L3 (L) (EXTRACT? OR PURIF? OR ISOLAT?)

SEA L4 AND VAT EXTRACT?

SEA L4 AND VAT

1 FILE SCISEARCH
18 FILE USPATFULL
1 FILE WPIDS
1 FILE WPINDEX

L5 QUE L4 AND VAT

FILE 'SCISEARCH' ENTERED AT 11:36:54 ON 02 NOV 2001

L6 1 S L5

=> index bioscience

FILE 'DRUGMONOG' ACCESS NOT AUTHORIZED
COST IN U.S. DOLLARS

FULL ESTIMATED COST

SINCE FILE	TOTAL
ENTRY	SESSION
5.94	21.39

INDEX 'ADISALERTS, ADISINSIGHT, ADISNEWS, AGRICOLA, ANABSTR, AQUASCI,
BIOBUSINESS, BIOCOMMERCE, BIOSIS, BIOTECHABS, BIOTECHDS, BIOTECHNO, CABA,
CANCERLIT, CAPLUS, CEABA-VTB, CEN, CIN, CONFSCI, CROPB, CROPU, DDFB,
DDFU, DGENE, DRUGB, DRUGLAUNCH, DRUGMONOG2, ...'

ENTERED AT 11:38:17 ON 02 NOV 2001

59 FILES IN THE FILE LIST IN STNINDEX

Enter SET DETAIL ON to see search term postings or to view
search error messages that display as 0* with SET DETAIL OFF.

=> s l4 (l) acid (l) neutraliz?

```
      4  FILE ANABSTR
      5  FILE BIOSIS
      2  FILE BIOTECHNO
12 FILES SEARCHED...
      24  FILE CAPLUS
19 FILES SEARCHED...
      5  FILE DRUGU
29 FILES SEARCHED...
      6  FILE EMBASE
      1  FILE ESBIODBASE
      4  FILE IFIPAT
40 FILES SEARCHED...
      1  FILE LIFESCI
      5  FILE MEDLINE
      1  FILE PASCAL
49 FILES SEARCHED...
      2  FILE PROMT
      4  FILE SCISEARCH
      1  FILE SYNTHLINE
      1  FILE TOXLIT
     870  FILE USPATFULL
58 FILES SEARCHED...
```

16 FILES HAVE ONE OR MORE ANSWERS, 59 FILES SEARCHED IN STNINDEX

L7 QUE L4 (L) ACID (L) NEUTRALIZ?

=> s l7 and (column? or chromatog? or hplc)

```
      3  FILE ANABSTR
      3  FILE BIOSIS
11 FILES SEARCHED...
      2  FILE BIOTECHNO
      9  FILE CAPLUS
17 FILES SEARCHED...
      1  FILE DRUGU
29 FILES SEARCHED...
      4  FILE EMBASE
38 FILES SEARCHED...
      1  FILE LIFESCI
      3  FILE MEDLINE
      1  FILE PASCAL
49 FILES SEARCHED...
      3  FILE SCISEARCH
     763  FILE USPATFULL
58 FILES SEARCHED...
```

11 FILES HAVE ONE OR MORE ANSWERS, 59 FILES SEARCHED IN STNINDEX

L8 QUE L7 AND (COLUMN? OR CHROMATOG? OR HPLC)

=> d rank

F1	763	USPATFULL
F2	9	CAPLUS
F3	4	EMBASE
F4	3	ANABSTR
F5	3	BIOSIS
F6	3	MEDLINE
F7	3	SCISEARCH
F8	2	BIOTECHNO
F9	1	DRUGU
F10	1	LIFESCI
F11	1	PASCAL

=> fil f2, f5, f6, f7, f10

COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	4.05	25.44

FILE 'CAPLUS' ENTERED AT 11:43:28 ON 02 NOV 2001
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PROCESSING COMPLETED FOR L9
L10 13 DUP REM L9 (6 DUPLICATES REMOVED)

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YOU HAVE REQUESTED DATA FROM 13 ANSWERS - CONTINUE? Y/(N):y

L10 ANSWER 1 OF 13 BIOSIS COPYRIGHT 2001 BIOSIS DUPLICATE 1
 AN 1995:71955 BIOSIS
 DN PREV199598086255
 TI Hair analysis for buprenorphine and its dealkylated metabolite by RIA and confirmation by LC/ECD.
 AU Kintz, Pascal (1); Cirimele, Vincent; Edel, Yves; Jamey, Carole; Mangin, Patrice
 CS (1) Inst. Med. Legale, 11 rue Humann, 67000 Strasbourg France
 SO Journal of Forensic Sciences, (1994) Vol. 39, No. 6, pp. 1497-1503. ISSN: 0022-1198.
 DT Article
 LA English
 AB Hair samples were obtained from 14 subjects admitted 2 or 3 months previously to a detoxification center. All reported an history of intravenous ***heroin*** abuse. After decontamination by two dichloromethane washes, about 50 mg hair were pulverized in a ball mill and incubated at 56 degree C overnight in 1 mL 0.1 HCl. After ***neutralization***, buprenorphine analyzed by RIA was in the range of 0.01 to 0.47 ng/mg. To confirm buprenorphine, liquid ***chromatography*** was used. After ***neutralization***, drugs were ***extracted*** with toluene at pH 8.5 during a 3-step ***extraction*** procedure. A portion of the reconstituted residue was injected into a Lichrosorb CN ***column***, with a mobile phase of phosphate buffer (pH 4.0)-acetonitrile-1-heptane sulfonic ***acid***-butylamine (85:17:2:0.01, v/v). Detection was achieved by coulometry, and the potential of the electrodes was 0.15 and 0.50 V, respectively. Linear calibration curves were obtained from 0.02 to 2.0 ng/mg with a correlation coefficient $r > 0.99$ for both drugs. The detection limit for the major metabolite was about 0.01 ng/mg and 0.02 ng/mg for buprenorphine, using a 50 mg hair sample. Recovery (at 0.2 ng/mg) was 54 and 62% for norbuprenorphine and buprenorphine, respectively. Drugs concentrations in hair were in the range 0.02-0.59 and not detected-0.15 ng/mg for buprenorphine and norbuprenorphine, respectively. Results suggest that a dose-response relationship exists between the concentration of buprenorphine in hair and the administered dose.
 CC General Biology - Forensic Science *00531
 Radiation - Radiation and Isotope Techniques *06504
 Behavioral Biology - Human Behavior *07004
 Biochemical Methods - General *10050
 Biochemical Studies - General *10060
 Psychiatry - Addiction - Alcohol, Drugs, Smoking, etc. *21004
 Pharmacology - Drug Metabolism; Metabolic Stimulators *22003
 Pharmacology - Clinical Pharmacology *22005
 Pharmacology - Neuropharmacology *22024
 Toxicology - Pharmacological Toxicology *22504
 Immunology and Immunochemistry - General; Methods *34502
 BC Hominidae *86215
 IT Major Concepts
 Behavior; Biochemistry and Molecular Biophysics; Forensics; Immune System (Chemical Coordination and Homeostasis); Methods and Techniques; Pharmacology; Psychiatry (Human Medicine, Medical Sciences); Radiology (Medical Sciences); Toxicology
 IT Chemicals & Biochemicals
 BUPRENORPHINE
 IT Miscellaneous Descriptors
 ANALYTICAL METHOD; DOSE-RESPONSE RELATIONSHIP; FORENSICS; HUMAN DRUG ABUSE; LIQUID ***CHROMATOGRAPHY*** /ELECTRON CAPTURE DETECTOR;

NARCOTICS; RADIOIMMUNOASSAY; TOXICOLOGY

ORGN Super Taxa
Hominidae: Primates, Mammalia, Vertebrata, Chordata, Animalia

ORGN Organism Name
Hominidae (Hominidae)

ORGN Organism Superterms
animals; chordates; humans; mammals; primates; vertebrates

RN 52485-79-7 (BUPRENORPHINE)

L10 ANSWER 2 OF 13 BIOSIS COPYRIGHT 2001 BIOSIS DUPLICATE 2

AN 1993:372875 BIOSIS

DN PREV199396058550

TI Opiate concentrations in human head, axillary, and pubic hair.

AU Kintz, Pascal (1); Mangin, Patrice

CS (1) Inst. Med. Legale, 11 rue Humann, 67000 Strasbourg France

SO Journal of Forensic Sciences, (1993) Vol. 38, No. 3, pp. 657-662.
ISSN: 0022-1198.

DT Article

LA English

AB The concentrations of ***morphine*** and ***codeine*** were investigated in hair from the head, axillary and pubic regions obtained from 12 fatal ***heroin*** cases. Hair preparation involves a decontamination procedure in dichloromethane at 37 degree C for 15 min, solubilization in sodium hydroxyde at 100 degree C for 5 min, ***neutralization*** with hydrochloric ***acid*** and centrifugation. After ***extraction*** in chloroform-isopropanol-n-heptane (50:17:33; v/v) at pH 9.2, drugs were derivatized with BSTFA + 1% TMCS and separated on a 12-m BP-5 capillary ***column***. Quantification was done by GC/MS using selected ion monitoring. The highest ***morphine*** concentrations were found in pubic hair (0.80 to 41.34 ng/mg), followed by hair of the head (0.62 to 27.10 ng/mg), and axillary hair (0.40 to 24.20 ng/mg). ***Codeine*** was also detected in all samples, and the ***codeine*** -to- ***morphine*** ratios ranged from 0.069 to 0.273. The differences observed in drug concentrations in the 3 types of hair are discussed in the light of the existing literature.

CC General Biology - Forensic Science *00531
Behavioral Biology - Human Behavior 07004
Clinical Biochemistry; General Methods and Applications *10006
Biochemical Studies - General 10060
Chordate Body Regions - Head *11304
Pathology, General and Miscellaneous - Diagnostic *12504
Reproductive System - Physiology and Biochemistry 16504
Integumentary System - Physiology and Biochemistry *18504
Psychiatry - Addiction - Alcohol, Drugs, Smoking, etc. *21004
Pharmacology - General *22002
Pharmacology - Drug Metabolism; Metabolic Stimulators *22003
Pharmacology - Neuropharmacology *22024
Pharmacology - Psychopharmacology *22026
Toxicology - Pharmacological Toxicology *22504

BC Hominidae *86215

IT Major Concepts
Clinical Chemistry (Allied Medical Sciences); Forensics; Integumentary System (Chemical Coordination and Homeostasis); Morphology; Pathology; Pharmacology; Psychiatry (Human Medicine, Medical Sciences); Toxicology

IT Chemicals & Biochemicals
CODEINE; MORPHINE

IT Miscellaneous Descriptors
 ANALYTICAL METHOD; FORENSIC TOXICOLOGY; PHARMACOKINETICS

ORGN Super Taxa
 Hominidae: Primates, Mammalia, Vertebrata, Chordata, Animalia

ORGN Organism Name
 human (Hominidae)

ORGN Organism Superterms
 animals; chordates; humans; mammals; primates; vertebrates

RN 76-57-3 (CODEINE)
 57-27-2 (MORPHINE)

L10 ANSWER 3 OF 13 BIOSIS COPYRIGHT 2001 BIOSIS DUPLICATE 3

AN 1994:211480 BIOSIS

DN PREV199497224480

TI Variability of opiates concentrations in human hair according to their anatomical origin: Head, axillary and pubic regions.

AU Mangin, Patrice (1); Kintz, Pascal

CS (1) Inst. de Med. Legale, 11 rue Humann, 67000 Strasbourg France

SO Forensic Science International, (1993) Vol. 63, No. 1-3, pp. 77-83.
 ISSN: 0379-0738.

DT Article

LA English

AB The concentrations of ***morphine*** and ***codeine*** were investigated in hair from the head, axillary and pubic regions obtained from 20 fatal ***heroin*** cases. Hair preparation involves decontamination procedure in dichloromethane at 37 degree C for 15 min, solubilization in sodium hydroxide at 100 degree C for 5 min, ***neutralization*** with hydrochloric ***acid*** and centrifugation. After ***extraction*** in chloroform/isopropanol/n-heptane (50:17:33; v/v) at pH 9.2, drugs were derivatized with BSTFA + 1% TMCS and separated on a 12-m BP-5 capillary ***column***. Quantification was done by GC/MS using selected ion monitoring. The highest ***morphine*** concentrations were found in pubic hair (0.80-41.34 ng/mg), followed by hair of the head (0.62-27.10 ng/mg), and axillary hair (0.40-24.20 ng/mg). ***Codeine*** was also detected in all samples, and the ***codeine*** / ***morphine*** ratios ranged from 0.054 to 0.273. The differences observed in drug concentration in the three kinds of hair are discussed in the light of the existing literature.

CC Biochemical Studies - General 10060
 Chordate Body Regions - Head *11304
 Chordate Body Regions - Pelvis *11316
 Metabolism - General Metabolism; Metabolic Pathways *13002
 Integumentary System - Anatomy *18502
 Integumentary System - Physiology and Biochemistry *18504
 Psychiatry - Addiction - Alcohol, Drugs, Smoking, etc. *21004

BC Hominidae *86215

IT Major Concepts
 Integumentary System (Chemical Coordination and Homeostasis);
 Metabolism; Morphology; Psychiatry (Human Medicine, Medical Sciences)

IT Chemicals & Biochemicals
 MORPHINE; CODEINE

IT Miscellaneous Descriptors
 CODEINE; MORPHINE

ORGN Super Taxa
 Hominidae: Primates, Mammalia, Vertebrata, Chordata, Animalia

ORGN Organism Name
 Hominidae (Hominidae)

ORGN Organism Superterms

animals; chordates; humans; mammals; primates; vertebrates

RN 57-27-2 (MORPHINE)

76-57-3 (CODEINE)

L10 ANSWER 4 OF 13 LIFESCI COPYRIGHT 2001 CSA

AN 94:54322 LIFESCI

TI Variability of opiates concentrations in human hair according to their anatomical origin: Head, axillary and public regions

AU Mangin, P.; Kintz, P.

CS Inst. Med. Legale, 11 rue Humann, 67000 Strasbourg, France

SO FORENSIC SCI. INT., (1993) pp. 77-83.

Meeting Info.: 1. International Meeting on Hair Analysis as a Diagnostic Tool for Drugs of Abuse. Genoa (Italy). 10-11 Dec 1992.

ISSN: 0379-0738.

DT Book

TC Conference

FS X

LA English

SL English

AB The concentrations of ***morphine*** and ***codeine*** were investigated in hair from the head, axillary and pubic region obtained from 20 fatal ***heroin*** cases. Hair preparation involves decontamination procedure in dichloromethane at 37 degree C for 15 min, solubilization in sodium hydroxide at 100 degree C for 5 min, ***neutralization*** with hydrochloric ***acid*** and centrifugation. After ***extraction*** in chloroform/isopropanol/n-heptane (50:17:33; v/v) at pH 9.2, drugs were derivatized with BSTFA + 1% TMCS and separated on a 12-m BP-5 capillary ***column***. Quantification was done by GC/S using selected ion monitoring. The highest ***morphine*** concentrations were found in pubic hair (0.80-41.34 ng/mg), followed by hair of the head (0.62-27.10 ng/mg), and axillary hair (0.40-24.20 ng/mg). ***Codeine*** was also detected in all samples, and the ***codeine*** / ***morphine*** ratios ranged from 0.054 to 0.273. The differences observed in drug concentration in the three kinds of hair are discussed in the light of the existing literature.

CC 24222 Analytical procedures; 24180 Social poisons & drug abuse; 24114 Metabolism

UT opiates; concentration; variation; hair; man; morphine; codeine

L10 ANSWER 5 OF 13 CAPLUS COPYRIGHT 2001 ACS

AN 1966:103109 CAPLUS

DN 64:103109

OREF 64:19317a-e

TI Ring opening of opium alkaloids by ion exchange

AU Buechi, J.; Moos, R. von

CS Eidg. Tech. Hochsch, Zurich, Switz.

SO Pharm. Acta Helv. (1966), 41(3), 142-63

DT Journal

LA German

CC 30 (Pharmaceuticals)

AB A review of the most important methods for the sepn. of the alkaloids is presented. Studies are concerned with the prepn. of the alkaloids and of the opium samples, choice and characteristics of ion-exchangers including pH values, speed of exchange, exchange equil., elution expts. with single alkaloids and with mixts. using Duolite C-25, Duolite C-10, Duolite CS 101, CAM L-124. The opium was extd. by ***column***

chromatography using Al₂O₃ and HCl. The alkaloids were sepd. by using 50 ml. of the ***acid*** ***purified*** opium ext. (= 0.5 g. opium), mixing with 2 g. Duolite C-10(NH₄ form), and ***neutralizing*** by the addn. of some drops of concd. ammonia. After shaking for 5 min., the resin with adsorbed alkaloids was washed with 200 ml. H₂O at 50.degree. and then filtered. Duolite C-10(NH₄-form) (5 g.) was allowed to soak in an eluting soln. of 100:60 MeOH-H₂O and placed in a ***chromatographic*** tube. After 30 min., elution with slight pos. pressure was conducted at the rate of 1 ml./min. Using MeOH-methylene chloride-buffer soln. pH 7 (100:50:60), 300 ml. contg. narcotine, ***papaverine***, and narceine were obtained. Then using an eluant of MeOH-methylene chloride-2N NH₄OH (100:50:60), 300 ml. eluate contg. ***morphine***, ***codeine***, thebaine, and cryptopine was collected. Narceine was sepd. from narcotine and ***papaverine*** by using Duolite CS 101 (NH₄ form); narceine eluted with MeOH:H₂O (15:85) and papavarine and narcotine with MeOH-methylene chloride-2N NH₄OH (100:50:2). Narcotine was sepd. from ***papaverine*** by hydrolyzing the lactone ring of narcotine and sepg. the resulting .gamma.-hydroxy carboxylic ***acid*** from ***papaverine***. Sepn. of ***morphine*** from thebaine and ***codeine*** was accomplished on Dowex (OH form); MeOH removed thebaine and ***codeine*** and 50% AcOH removed ***morphine***. For the quant. detn. of the opium alkaloids after their

sepn., the eluate is evapd. to dryness on a steam bath and the residue taken up with 10 ml. 2N AcOH and 10 ml. freshly prepd. satd. reineckate soln. is added; after standing for 60 min. the ppt. is filtered off by suction and washed with ice H₂O. The reineckate is dissolved in a min. amt. of acetone, transferred to a 25-ml. flask, 2 ml. alk. Fehling no. 2 soln. and 40 ml. H₂O are added followed by boiling for 10 min. To the cold soln. is added 20 ml. 25% HNO₃ and 10 ml. 0.1N AgNO₃; the excess AgNO₃ is backtitrated with 0.1N NH₄CNS soln. and the endpoint detd. electrometrically. The results obtained compare favorably with other methods and is preferred to the method of Anneler (CA 14, 3499). 49 references.

L10 ANSWER 6 OF 13 CAPLUS COPYRIGHT 2001 ACS

AN 1960:28745 CAPLUS

DN 54:28745

OREF 54:5654c-i,5655a-h

TI Synthesis of isoquinoline derivatives

AU Tachikawa, Ryuji

CS Univ. Tokyo

SO Tetrahedron (1959), 7, 118-22

DT Journal

LA Unavailable

CC 10G (Organic Chemistry: Heterocyclic Compounds)

GI For diagram(s), see printed CA Issue.

AB The Bischler-Napieralski reaction was applied to the synthesis of several ***papaverine*** derivs. (I, R = R₁, R₂ = OMe, n = 1; R = Me, R₁ = H, R₂R₂ = O₂CH₂, n = 1; R = Me, R₁ = H, R₂R₂ = O₂CH₂, n = 0; R = H, R₁ = R₂ = OMe, n = 1) (II, III, IV, V), devoid of 1 or 2 MeO groups in positions 6 and 7. C₆H₆ (80 ml.) contg. 6.2 g. .beta.-cyclohexa-1,4-dienylethylamine stirred with cooling and dropwise addn. of freshly distd. 3,4-(MeO)₂C₆H₃CH₂COCl in 100 ml. C₆H₆ in the presence of 200 ml. 5% NaHCO₃ and the amide kept in soln. by addn. of EtOAc, the mixt. stirred 2 hrs. at room temp. and the supernatant layer evapd. yielded 13.8 g. N-(3,4-dimethoxyphenylacetyl)-.beta.-cyclohexa-1,4-dienylethylamine (VI),

m. 111-12.degree. (C₆H₆C₆H₁₄). VI (2.0 g.) in 30 ml. C₆H₆ refluxed gently 30 min. with 2 ml. POCl₃ and the solvent evapd. in vacuo, the residue taken up in dil. HCl and the soln. basified, the product (1.8 g.) refluxed 3 hrs. (N atm.) in 30 ml. xylene with 0.4 g. 30% Pd-C, the filtered soln. evapd. and the residue distd. in vacuo gave 1.65 g. viscous 1-(3,4-dimethoxybenzyl)-3,4-dihydroisoquinoline, b_{0.08} 194-7.degree., .lambda. 271, 312, 323 m.mu. (log .epsilon. 3.81, 3.31, 3.33, alc.) [picrate m. 154-5.degree. (alc.)], also obtained by refluxing 6.0 g. N-(3,4-dimethoxyphenylacetyl)-.beta.-phenylethylamine 6.5 hrs. with 200 ml. xylene and 30 g. P₂O₅ and ***purifying*** the product by filtration through Al₂O₃. The base (2.0 g.) in 20 ml. Et cinnamate heated (N atm.) 2.5 hrs. over 0.2 g. 30% Pd-C and the cooled mixt. filtered, the filtrate and C₆H₆ washings shaken with 10% HCl and the ***acid*** soln. basified, the sirupy base (1.73 g.) ***chromatographed*** over Al₂O₃ in C₆H₆ and the product (1.52 g.) crystd. from C₆H₁₄ gave II, m. 71-2.degree., .lambda. 274, 311, 323 m.mu. (log .epsilon. 3.76, 3.49, 3.54, alc.); picrate m. 164.degree. (alc.). MeCH:CHPh (30 g.) in 250 ml. Et₂O and aq. NaNO₂ (120 g.) stirred and cooled with dropwise addn. of 410 g. 20% H₂SO₄ and the stirring contg. 1 hr., the product washed with H₂O, MeOH and Et₂O and dried yielded 26.3 g. corresponding pseudonitrosite (VII), m. 116-18.degree. (decompn.). VII (15 g.) added portionwise to 100 ml. 10% KOH in MeOH and the soln. ***neutralized*** with AcOH, the solvent evapd. in vacuo and the inorg. matter dissolved in H₂O, the oily product taken up in C₆H₆ and the washed and dried soln. evapd. gave 12.5 g. PhCHMeCHMeNO₂, b₅ 112-14.degree.. LiAlH₄ (6 g.) in cold Et₂O stirred with dropwise addn. of 13.8 g. nitro compd. in Et₂O and dild. with cold H₂O, the Et₂O evapd. and the oily base taken up in HCl, shaken with C₆H₆ and basified with concd. NaOH, the C₆H₆ soln. dried and evapd. and the residue distd. (H atm.) in vacuo gave 8.8 g. PhCH(OMe)CHMeNH₂, b₆ 93-5.degree.; HCl salt m. 186-8.degree. (alc. Me₂CO). The amine (6.6 g.) in 18.3 g. abs. alc. and 100 ml. liquid NH₃ reduced by portionwise addn. of 2.8 g. Li with cooling in alc. and solid CO₂, the mixt. stirred until the blue color disappeared and the base distd. in vacuo (H atm.) yielded 5.2 g. 3-(cyclohexa-1,4-dienyl)-2-aminopropane (VIII), b₅ 71-2.degree.. Condensation of VIII with 3,4-(CH₂O₂)C₆H₃CH₂COC₁ formed N-(3,4-methylenedioxyphenylacetyl)-.beta.-cyclohexa-1,4-dienylisopropylamine, m. 108-9.degree. (C₆H₁₄-C₆H₆), cyclized and dehydrogenated to 1-(3,4-methylenedioxybenzyl)-3-methyl-3,4-dihydroisoquinoline, 276, 318, 326 m.mu. (log 3.80, 3.46, 3.44, alc.) [picrate m. 170-1.degree. (decompn.)], further dehydrogenated in boiling PhCH:CHCO₂Et by Pd-C to colorless prisms of III, m. 87-8.degree. (C₆H₁₄), .lambda. 278, 317, 329 m.mu. (log .epsilon. 3.89, 3.54, 3.56, alc.); picrate m. 180.degree. (alc. AcOH). Similarly condensation of VIII with 3,4-(CH₂O₂)C₆H₃COC₁ gave N-(3,4-methylenedioxybenzoyl)-.beta.-cyclohexa-1,4-dienylisopropylamine, m. 83-4.degree. (C₆H₁₄), cyclized and dehydrogenated to 1-(3,4-methylenedioxyphenyl)-3-methyl-3,4-dihydroisoquinoline, .lambda. 259 293 m.mu. (log .epsilon. 3.95, 3.83, alc.); picrate, m. 175-6.degree. (decompn.). Further dehydrogenation as for III yielded 72.5% IV, m. 74-5.degree. (C₆H₁₄), .lambda. 285, 333 m.mu. (log .epsilon. 3.96, 3.87, alc.); picrate, m. 184.degree. (alc.). Redn. of 4-MeOC₆H₄CH₂CH₂NH₂ according to Birch (C.A. 52, 18525b) and distn. (H atm.) gave colorless .beta.-(4-methoxycyclohexa-1,4-dienyl)ethylamine, b_{1.0} 78-8.5.degree., .lambda. 277 m.mu. (log .epsilon. 1.72), treated with 3,4-(MeO)₂C₆H₃CH₂COC₁ to yield 90.2% N-(3,4-dimethoxyphenylacetyl)-.beta.-cyclohexa-1,4-dienylethylamine (IX), m. 91-3.degree. (C₆H₆-C₆H₁₄). IX (2 g.) in 50 ml. C₆H₆ and 2 ml. POCl₃ refluxed 10-15 min. on a steam bath and the cooled mixt. dild. with petr. ether, the base extd. with C₆H₆ and

shaken vigorously with 100 ml. 10% NaOH, the C₆H₆ layer dried over K₂CO₃ and the solvent evapd. (N atm.) in vacuo, the brown sirup refluxed 4 hrs. (N atm.) in abs. xylene over 0.5 g. 30% Pd-C and the filtered soln. evapd. in vacuo, the residue taken up in 10% HCl and extd. with C₆H₆, basified with NaOH soln. and the washed and dried ext. evapd. in vacuo, the residue filtered in C₆H₆-C₆H₁₄ through Al₂O₃ and the filtrate evapd. gave 0.21 g. 1-(3,4-dimethoxybenzyl)-7-methoxy-3,4-dihydroisoquinoline (X), λ . 277, 310, 321 m. μ . (log ϵ . 3.83, 3.37, 3.89, alc.); picrate m. 159-61.degree. (decompn.) (Me₂CO). Dehydrogenation of X yielded 60.4% V, m. 85-6.degree. (C₆H₁₄), λ . 277, 313, 323 m. μ . (log ϵ . 3.85, 3.61, 3.63, alc.); picrate m. 171.degree. (alc. AcOH). The reddish oil, obtained by cyclizing IX with POCl₃ acidified with 10% HCl and washed with C₆H₆, the ***acid*** soln. warmed several min. with C₆H₆ on a steam bath and the cooled mixt. basified with aq. Na₂CO₃, the washed and dried C₆H₆ layer concd. and the residue filtered through Al₂O₃, the filtrate evapd. and the base crystd. (C₆H₁₄-Me₂CO) yielded 39.8% 1-(3,4-dimethoxybenzyl)-7-oxo-3,4,4a,5,6,7-hexahydroisoquinoline (XI), m. 176-8.degree., ν . 1668 cm.⁻¹ (Nujol); 2,4-dinitrophenylhydrazone sulfate m. 212-14.degree. (decompn.) (alc.). XI (0.6 g.) in 4 ml. CH(OMe)₃ cooled and satd. with HCl, the mixt. refluxed 2.5 hrs. and excess CH(OMe)₃ distd., the residue kneaded with 2 g. K₂CO₃ and covered with Et₂O, cooled and treated with 20 ml. 5% K₂CO₃, the aq. layer extd. with Et₂O and the product filtered in C₆H₆-C₆H₁₄ through Al₂O₃ gave 0.32 g. 1-(3,4-dimethoxybenzyl)-7,7-dimethoxy-3,4,4a,5,6,7-hexahydroisoquinoline (XII); MeI salt m. 198-201.degree. (decompn.) (alc.). XII (0.25 g.) in a small amt. of C₆H₆ mixed with a few drops of (tert-BuO)₃Al in C₆H₆ and the solvent evapd., the residue heated (N atm.) 2 hrs. at 200-20.degree. and extd. with C₆H₆, taken up in C₆H₁₄ and filtered through Al₂O₃, the filtrate evapd. and the oily product (0.11 g.) dehydrogenated in boiling PhCH:CHCO₂Et over Pd-C gave 0.05 g. V, m. 85-6.degree..

L10 ANSWER 7 OF 13 CAPLUS COPYRIGHT 2001 ACS

AN 1958:98073 CAPLUS

DN 52:98073

OREF 52:17301g-i,17302a-i,17303a-i,17304a-i,17305a-g

TI Constitution of yohimbine and related alkaloids. X. Synthesis of 12H-indolo[2,3-a]pyridocolinium salts, including flavocoryline and flavopereirine

AU Prasad, K. B.; Swan, G. A.

CS Univ. Durham, Newcastle-upon-Tyne, UK

SO J. Chem. Soc. (1958) 2024-38

DT Journal

LA Unavailable

CC 10H (Organic Chemistry: Alkaloids)

GI For diagram(s), see printed CA Issue.

AB cf. C.A. 50, 13918g. In a new synthetic route to rings A, B, C and D of the yohimbine skeleton with or without ring E some 12H-indolo[2,3-a]pyridocolines salts (I) of indolo[2,3-a]pyridocolines (II) were synthesized, as well as a homolog (III) of alstyrine. Et₂O (50 ml.) contg. 2.5 g. 2-NCC₅H₄N added in 10 min. with stirring at 0.degree. to EtO(CH₂)₃MgBr (1.2 g. Mg, 8 g. EtO(CH₂)₃Br, 30 ml. Et₂O) and the mixt. refluxed 3 hrs., cooled to 0.degree., and stirred with gradual addn. of 20 ml. H₂O and 70 ml. 5N H₂SO₄, the Et₂O layer extd. twice with 70 ml. 2N H₂SO₄, the ***acid*** exts. heated 20 min. on a steam bath, the cooled soln. basified with satd. aq. K₂CO₃ and extd. with CHCl₃, the ext. dried (K₂CO₃) and distd. (method A) gave 3.2 g. liquid imine (IV), 2-EtO(CH₂)₃C(:NH)C₅H₄N, b_{0.6} 90-8.degree., b₁₁ 145.degree., ν . 3376,

1681 cm.⁻¹, also obtained (2.25 g.) by decomp. the Grignard complex with 30 ml. 1:1 concd. HCl-H₂O and omitting the subsequent heating (method B). BuLi in Et₂O (8 ml.) (1 ml. equiv. to 1.44 ml. N HCl) stirred at -50.degree. (N atm.) with addn. of 2 g. 2-BrC₅H₄N in Et₂O and after stirring 15 min. treated with 2 g. EtO(CH₂)₃CN in Et₂O, the mixt. kept 15 min. at -50.degree. and warmed gradually to room temp., stirred 1 hr. and dild. with 15 ml. H₂O and 8 ml. 2N H₂SO₄, the Et₂O layer worked up as above and the product (0.75 g.) distd. gave IV, b. 150.degree.. The samples of IV treated with warm alc. 2,4-(O₂N)₂C₆H₃NHNH₂ contg. a few drops of HBr gave the HBr salt, m. 197.degree., converted by shaking with CHCl₃ and dil. aq. Na₂CO₃ and evapg. the dried (Na₂SO₄) CHCl₃ layer to 2- γ -ethoxybutyrylpyridine 2,4-dinitrophenylhydrazone, m. 137.degree. (C₆H₆-petr. ether). IV (3 g.) refluxed 15 hrs. with 18 ml. AcOH and 9 ml. 47.5% HBr in a stream of N and the mixt. evapd. at 100.degree./14 mm., the residue taken up in a small vol. of MeOH and dild. with Me₂CO gave 2.75 g. 1,2,3,4-tetrahydro-1-oxopyridocolinium bromide (V), m. 205.degree. (decompn.); picrate, m. 147-8.degree. (alc.); 2,4-dinitrophenylhydrazone, m. 192.degree. (decompn.) (alc.), 249-50.degree. (decompn.) (AcOH), giving with dil. NaOH a deep blue-violet color, sol. in CHCl₃. V (1.5 g.), 0.9 g. PhNHNH₂.HCl, and 3 g. cryst. NaOAc in sep. solns. in a min. of H₂O heated together 3 hrs. on a steam bath and the cooled soln. filtered, the solid (2.1 g.) washed with H₂O and crystd. (EtOH-Et₂O) gave the bromide phenylhydrazone (Va), C₁₅H₁₆BrN₃.0.5 H₂O, m. 271.degree. (decompn.); IV phenylhydrazone picrate, C₂₁H₁₃N₆O₇, m. 225.degree. (decompn.) (HCONMe₂-EtOH). Va (1.5 g.) in 45 ml. abs. alc. at 0.degree. satd. with dry HCl and kept 1 hr. at room temp., the mixt. refluxed 5 hrs. and kept overnight at 0.degree., filtered and the product washed with ice-cold alc. gave 1.2 g. 6,7-dihydro deriv. of I (VI, R = H, X = Cl) (VII), m. 340.degree. (decompn.) (MeOH-EtOH), λ_{max} . 2170, 2520, 3140. 3850 A. (log ϵ . 4.35, 3.93, 4.15, and 4.16), λ_{min} . 2390, 2745, 3410 A. (log ϵ . 3.83, 3.42, 3.89) in alc. HCl; λ_{max} . 2230, 2645, 3630, 4200 A. (log ϵ . 4.37, 4.40, 4.09, 4.19), λ_{min} . 2490, 2940, 3780 A. (log ϵ . 3.87, 3.55, 4.06) in 0.015N alc. KOH; picrate, m. 249.degree. (decompn.) (HCONMe₂-MeOH); nitrate, m. 259.degree. (decompn.) (alc.). A Fischer indole reaction with the use of polyphosphoric ***acid*** according to Sugawara, et al. (C.A. 51, 3593d), converted 2-MeC(:NNHPh)C₅H₄N into 2,2'-pyridylindole (VIII), heated 20 hrs. at 100.degree. with excess MeI and the mixt. dild. with Et₂O to give VIII MeI salt, m. 238.degree. (MeOH). VII (80.6 mg.) in 10 ml. AcOH hydrogenated 4 hrs. at 18.degree./760 mm. with freshly reduced PtO₂ and the warm filtered soln. evapd. at 100.degree./14 mm. gave the HCl salt, m. 302.degree. (decompn.) (alc.), basified in H₂O with NaOH to give 1,2,3,4,6,7,12,12b-octahydro-12H-indolo[2,3-a]pyridocoline (IX), m. 150.degree. (ligroine) (cf. C.A. 46, 9569e). The ultraviolet absorption spectra in ***acid*** and alk. solns. were measured and corresponded with a change in structure. For comparison the spectra of VIII and 2,4'-pyridylindole and their respective MeI salts were shown. It was shown that the change in structure of VII in alk. soln. depended on the H atom attached to the indole-N atom. V (0.25 g.) treated with 0.17 g. PhNMeNH₂ in the presence of 1.5 ml. N HCl and 0.75 g. NaOAc as above and the product ***isolated*** by addn. of satd. aq. KI gave 0.37 g. 1,2,3,4-tetrahydro-1-oxopyridocolinium 1-methyl-1-phenylhydrazone iodide, C₁₆H₁₈IN₃, m. 203.degree. (alc.), subjected to a Fischer indole reaction and the soln. concd. to one third vol., kept at 0.degree. and the filtered soln. evapd. at 100.degree./14 mm., the residue taken up in H₂O, the filtered soln. treated with satd. aq. KI, the ppt. washed with H₂O and recrystd. (MeOH) to give VI (R = Me, X = I) (X), m. 295.degree.

(decompn.), λ_{max} . 2120, 2510, 3150, 3780 and λ_{min} . 2400, 2760, 3370 Å. (log ϵ . 2.60, 4.07, 4.10, 4.21, and 3.99, 3.38, 3.95, in ***acid***); λ_{max} . 2530, 3150, 3770 and λ_{min} . 2400, 2750, 3380 Å. (log ϵ . 4.06, 4.09, 4.19 and 3.97, 3.34, 3.92, in alkali), also obtained by treating aq. VII with 40% NaOH and filtering, washing the ppt. with cold H₂O, and drying 2 days in vacuo, keeping the residue overnight with excess MeI, refluxing the mixt. 1 hr., evapg, and recrystg. (MeOH) the residue twice. The spectrum of X was almost identical with that of VII in ***acid*** soln. and did not change on addn. of alkali. Attempts to dehydrogenate VII by heating with acidic Pd-C according to Schwyzer (C.A. 47, 4347g) and by refluxing with chloranil in BuOH or shaking with O in AcOH in the presence of prerduced PtO₂ were unsuccessful. IX (50 mg.) and 100 mg. acidic Pd-C heated to 260.degree. in 20 min. with evolution of H between 200 and 260.degree., the cooled mixt. extd. with MeOH, the ext. evapd., and the residue taken up in warm dil. HCl, the soln. basified with aq. NH₄OH and extd. with Et₂O, the dried ext. (K₂CO₃) evapd., and the oily residue recrystd. (C₆H₆-ligroine) (C) gave 20 mg. 1-butyl-.beta.-carboline, C₁₅H₁₆N₂, m. 166.degree., λ_{max} . 2550, 2900, 3340, 3500, and λ_{min} . 2680, 3000, 3450 Å. (log ϵ . 4.61, 4.24, 3.73, 3.75 and 3.73, 3.10, 3.68, in alc.), showing a blue-violet fluorescence in very dil. ***acid*** solns. (cf. Spenser, C.A. 51, 2785e). VII was successfully dehydrogenated by use of high-potential quinone according to Braude, et al. (C.A. 49, 13150c). VII (80 mg.) in 10 ml. alc. refluxed 15 hrs. with 0.4 g. tetrachloro-.omicron.-benzoquinone, the solvent evapd., and the residue crystd. (MeOH-Et₂O) yielded 35 mg. I (R = H, X = Cl) (XI), C₁₃H₁₁ClN₂.H₂O, m. 295.degree. (decompn.), λ_{max} . 2440, 2940, 3450, 3880 and λ_{min} . 2680, 3050, 3770 Å. (log ϵ . 4.43, 4.12, 4.27, 4.10 and 3.96, 4.03, 4.05, in ***acid***); λ_{max} . 2270, 2410, 2890, 3200, 3490, 3700, 4490 and λ_{min} . 2370, 2620, 3100, 3280, 3600, 4180 Å. (log ϵ . 4.42, 4.32, 4.43, 4.09, 4.26, 4.22, 3.63 and 4.30, 4.13, 4.02, 4.19, 3.57, in alkali); picrate, m. 252-3.degree. (decompn.) (HCONMe₂-EtOH). The corresponding iodide prepd. as above for X and recrystd. (MeOH) 4 times gave I (R = H, X = I) (XII), m. 360.degree. (decompn.), λ_{max} . 2240, 2480, 2930, 3360, 3990 and λ_{min} . 2450, 2830, 3050, 3760 Å. (log ϵ . 4.52, 4.31, 4.08, 4.27, 4.07 and 4.30, 4.01, 3.98, 3.96, in neutral soln.); λ_{max} . 2250, 2530, 3300, 4000 and λ_{min} . 2460, 2830, 3780 (log ϵ . 4.51, 4.33, 4.27, 4.08 and 4.30, 4.05, 4.00, in alkali). The absorption spectra of XI in neutral and ***acid*** soln. corresponded to structures I and II, resp., and resembled very closely those of sempervirine under similar conditions. XI and VII showed a striking difference in dil. soln. under ultraviolet irradiation, the former and its homologs appearing brilliantly blue and the latter greenish-yellow. The slow disappearance of the 2390 Å band on storage was considered to indicate the slow formation of a pseudo-base in alk. soln. II (R = R' = Et) (XIII) was synthesized by the above route from 2,4,5-NC(Et)₂C₅H₂N (XIV). XIV [3 g., prepd. by improved modifications of the procedure of Lee and Swan (C.A. 50, 13918g)] treated with EtO(CH₂)₃MgBr (1.5 g. Mg and 10 g. EtO(CH₂)₂Br in 40 ml. Et₂O) gave 2.8 g. imine, C₁₅H₂₄N₂O, b_{0.2} 132-40.degree., ν . 3354 cm.⁻¹; 2-.gamma.-ethoxybutyryl-4,5-diethylpyridine 2,4-dinitrophenylhydrazone hydrobromide, C₂₁H₂₇N₅O₅.HBr, m. 202.degree. (decompn.), ***neutralized*** to the corresponding base, C₂₁H₂₇N₅O₅, m. 109-10.degree. (C₆H₆-ligroine). The imine (1 g.) refluxed 21 hrs. with AcOH-HBr and the amorphous product taken up in a min. of H₂O, basified with Na₂CO₃, and extd. with CHCl₃, the dried (Na₂SO₄) ext. evapd., and the oil (0.8 g.) converted into 0.5 g. 7,8-diethyl-1,2,3,4-tetrahydro-1-

phenylhydrazonopyridocolinium bromide, m. 255.degree. (Et₂O-EtOH), transformed (55 mg.) by the Fischer indole reaction to 35 mg. 2,3-diethyl-6,7-dihydro-12H-indolo[2,3-a]pyridocolinium chloride (XIVa), C₁₉H₂₁ClN₂·1.5H₂O, m. 273.degree. (decompn.) (alc.), .lambda.max. 2220, 3120, 3880 and .lambda.min. 2760, 3390 A (log .epsilon. 4.41, 4.19, 4.20 and 3.51, 3.94, in ***acid***; .lambda.max. 2300, 2630, 3610, 4110 and .lambda.min. 2520, 2920, 3740 A (log .epsilon. 4.44, 4.01, 4.13, 4.23 and 3.95, 3.50, 4.12, in alkali); picrate, m. 253.degree. (EtOH-Me₂CO); nitrate, m. 262-3.degree. (EtOH). XIVa dehydrogenated with tetrachloro-.omicron.-benzoquinone gave 2,3-diethyl-12H-indolo[2,3-a]pyridocolinium chloride, C₁₉H₁₉ClN₂·1.5 H₂O, m. 258.degree. (decompn.) (EtOH-Et₂O), .lambda.max. 2380, 2910, 3460, 3850 and .lambda.min. 2750, 3050, 3740 A (log .epsilon. 4.52, 4.15, 4.30, 4.24 and 4.04, 4.05, 4.16, in ***acid***); .lambda.max. 2310, 2410, 2880, 3180, 3640, 4400 and .lambda.min. 2370, 2650, 3090, 3260, 4190 A (log .epsilon. 4.43, 4.42, 4.44, 4.07, 4.31, 3.74 and 4.41, 4.14, 4.03, 4.05, 3.72, in alkali). Basification of the chloride in H₂O and ***chromatography*** of the product in CHCl₃ over Al₂O₃ gave XIII, C₁₉H₁₈N₂·1.5 H₂O, m. 150-1.degree. (MeOH); perchlorate, m. 301.degree. (decompn.), identical with flavocoryline perchlorate (cf. Goutarel, et al., C.A. 49, 10953i). II (R = iso-PrO, R' = Et) (XV) was also synthesized from 2,5,4-NC(Et)(iso-PrO)C₅H₂N (XVI). MeMgI (4.1 g. Mg, 24.3 g. MeI, and 125 ml. Et₂O) treated dropwise with stirring in 10 min. with 10.8 g. 5,2,4-EtMe(AcO)C₅H₂N in 100 ml. Et₂O at room temp. and the mixt. refluxed 3 hrs. with stirring, cooled in ice and decompd. with 210 ml. said NH₄Cl soln. and 35 ml. concd. HCl, basified with 10% aq. NaOH and extd. with CHCl₃, the dried (Na₂SO₄) ext. evapd. and the tertiary alc. (11.8 g.) refluxed 6 hrs. with 4.5 g. red P in 86 ml. 47.5% HI, the mixt. dild. with H₂O and the filtered soln. basified with 20% aq. NaOH, extd. with CHCl₃, and the dried (Na₂SO₄) ext. evapd. gave 9.2 g. XVI, b₂₀ 105-6.degree.; picrate, m. 179-80.degree. (alc.). XVI (10.5 g.) condensed with BzH by refluxing 96 hrs. in the procedure according to L. and S. (loc. cit.) yielded 10.5 g. 5,4,2-Et(iso-Pr)(PhCH:CH)C₆H₂N (XVII), b. 184-94.degree.; picrate, m. 235-6.degree. (decompn.) (alc.-HCONMe₂). XVII (10.5 g.) oxidized and the BzOH removed, the soln. evapd. at 100.degree./14 mm. and the residue taken up in abs. alc., the filtered soln. evapd. and the residue in 150 ml. alc. satd. with dry HCl at 0.degree., the mixt. kept overnight at room temp. and refluxed 4 hr., the soln. evapd. at 100.degree./14 mm. and the cooled residue taken up in H₂O, the soln. basified with satd. aq. Na₂CO₃ and extd. with CHCl₃ gave 5.2 g. 5,4,2-Et(iso-PrO)C₅H₂NCO₂Et (XVIII), b_{0.5} 125-9.degree.; picrate, m. 111.degree. (alc.). XVIII (0.45 g.) refluxed 5 hrs. in 10 ml. alc. with 2.5 ml. 40% aq. KOH and the soln. evapd., washed with Et₂O, adjusted to pH 4 with dil. HCl, extd. 30 hrs. with Et₂O, and the ext. evapd. gave 0.23 g. 5,4,2-Et(iso-PrO)C₅H₂NCO₂H, m. 147.degree. (MeOH-Et₂O), unchanged by sublimation at 60-80.degree./0.01 mm., .lambda.max. 2670, 2340 and .lambda.min. 2525 A (log .epsilon. 3.64, 3.78 and 3.48). The ***acid*** heated with Cu powder and the dillate treated with picric ***acid*** gave 3,4-Et(iso-PrO)C₅H₃N.C₆H₃N₃O₇, m. 136-7.degree. (alc.) (cf. Karrer and Mainoni, C.A. 48, 2720i). XVIII (4.9 g.) shaken 72 hrs. with 49 ml. aq. NH₄OH (d. 0.88) and the product (3.8 g.) sublimed at 60-80.degree./0.01 mm. gave 5,4,2-Et(iso-PrO)C₅H₂NCONH₂, m. 164-5.degree., dehydrated in 3.5 hrs. to 2.75 g. 5,4,2-Et(iso-PrO)C₅H₂NCN (XVIIIa), b_{0.2} 113-17.degree., converted by treatment with EtO(CH₂)₃MgBr to 5,4,2-Et(iso-PrO)C₅H₂NCO(CH₂)₃OEt (XIX), C₁₆H₂₅NO₂, b_{2.0} 165.degree.; 2,4-dinitrophenylhydrazone, m. 94.degree. (ligroine). XIX (1.15 g.) treated as above with HBr and the soln. evapd. gave 0.34 g. 2-.gamma.-bromobutyl-5-ethyl-4-isopropylpyridine hydrobromide, m.

150-1.degree. (MeOH-Me₂CO), which taken up in H₂O the soln. basified with Na₂CO₃, extd. with Et₂O, and the dried (K₂CO₃) ext. evapd. gave 7-ethyl-1,2,3,4-tetrahydro-1-phenylhydrazono-8-isopropylpyridocolinium bromide (XX), C₂₀H₂₆BrN₃·0.5 H₂O, m. 256-7.degree. (alc.-Et₂O), also produced by evapg. the above MeOH-Me₂CO mother-liquor and treating the residue with PhNHNH₂. XX submitted to the Fischer indole reaction gave the 3,2-Et(iso-PrO) deriv. of VI (R = H, X = Cl) (XXI), C₂₀H₂₃ClN₂·0.5 H₂O, m. 260.degree. (decompn.) (alc.-Et₂O), .lambda.max. 2220, 3140, 3880 and .lambda.min. 2750, 3410 A (log .epsilon. 4.44, 4.25, 4.22 and 3.58, 3.97, in ***acid***); .lambda.max. 2310, 2660, 3600, 4110 and .lambda.min. 2520, 2910, 3770 A (log .epsilon. 4.45, 4.04, 4.16, 4.23 and 3.95, 3.41, 4.13, in alkali). Dehydrogenation of XXI with tetrachloro-.omicron.-benzoquinone yielded the corresponding 3,2-Et(iso-PrO) deriv. of I (R = H, X = Cl) (XXII), C₂₀H₂₁ClN₂·H₂O, m. 270.degree. (decompn.) (alc.-Et₂O), .lambda.max. 2400, 2920, 3460, 3860 and .lambda.min. 2760, 3050, 3750 A (log .epsilon. 4.55, 4.15, 4.29, 4.25 and 3.99, 4.02, 4.16, in ***acid***); .lambda.max. 2310, 2890, 3180, 3610, 4420 and .lambda.min. 2620, 3090, 3280, 4180 A (log .epsilon. 4.43, 4.07, 4.30, 3.71 and 4.12, 4.01, 4.03, 3.67, in alkali). XXII in H₂O basified yielded XV, C₂₀H₂₁ClN₂·H₂O, m. 117-19.degree. (alc.). XXI (0.2 g.) and 0.35 g. tetrachloro-.omicron.-benzoquinone heated 8 hrs. on a steam bath in 2.5 ml. AcOH, the cooled mixt. dild. with Et₂O, filtered, the Et₂O-washed residue taken up in CHCl₃ and aq. NaOH, the dried (K₂CO₃) CHCl₃ layer evapd., the residue taken up in alc. contg. HCl, the mixt. dild. with Et₂O and filtered, the solid taken up in H₂O, the soln. treated with NH₄OH, the ppt. ***chromatographed*** in CHCl₃ over Al₂O₃, and the product recrystd. from MeOH gave XV, m. 204, recrystd. (MeOH) to a product of apparently the same compn., m. 149.degree. (for comparison of XV with flavocorynanthryrine, cf. Schwyzer, loc. cit.). The alkaloid flavopereirine, assigned the structure II (R = H, R' = Et) (XXIIa) by Bejar, et al. (C.A. 51, 14768c), was synthesized from 2,5-NCeC₅H₃N (XXIII). XXIII (1.77 g.) treated with EtO(CH₂)₃MgBr gave 1.77 g. 5,2-EtC₅H₃NCO(CH₂)₃OEt, b₃ 150-60.degree., converted (1.65 g.) with HBr and further treatment to 1.22 g. pyridocolinium bromide phenylhydrazono, m. 279.degree. (alc.-Et₂O). The Fischer indole reaction transformed 0.5 g. hydrazono to 0.33 g. chloride (XXIV), converted to the 3-Et deriv. of VI (R = H, X = NO₃), C₁₇H₁₇N₃O₃, m. 267.degree. (decompn.) (alc.), .lambda.max. 2130, 2520, 3160, 3950, and .lambda.min. 2430, 2750, 3450 A. (log .epsilon. 4.41, 3.95, 4.21, 4.16, and 3.88, 3.55, 3.92, in ***acid***), .lambda.max. 2220, 2670, 3600, 4230, and .lambda.min. 2490, 2950, 3830 A. (log .epsilon. 4.40, 4.01, 4.09, 4.21, and 3.83, 3.32, 4.05, in alkali). XXIV (0.13 g.) heated 9 hrs. on a steam bath with 0.23 g. tetrachloro-.omicron.-benzoquinone in 2 ml. AcOH and worked up as above, the dehydrogenated chloride tn up in MeOH, and treated with HClO₄ gave 38 mg. authentic XXIIa perchlorate, C₁₇H₁₅ClN₂O₄·HClO₄, m. 331.degree. (decompn.), .lambda.max. 2350, 2950, 3500, 3900, and .lambda.min. 2730, 3090, 3820 A. (log .epsilon. 4.52, 4.21, 4.32, 4.20, and 4.03, 4.07, 4.16, in ***acid***), .lambda.max. 2300, 2350, 2890, 3200, 3600, 4500, and .lambda.min. 2320, 2670, 3100, 3300, 4200 A. (log .epsilon. 4.46, 4.45, 4.49, 4.10, 4.33, 3.68, and 4.44, 4.14, 4.08, 4.05, 3.62, in alkali). The availability of XVIIIa provided an opportunity for the synthesis of III, 3-ethyl-2-(5-ethyl-4-isopropyl-2-pyridyl)indole. XVIIIa (0.81 g.) treated with PrMgBr gave 0.3 g. 5,4,2-Et(iso-PrO)C₅H₂NCOPr, b_{1.0} 80-90.degree., converted by Fischer indole synthesis to material, b_{0.3} 184-95.degree. triturated with ligroine and recrystd. (MeOH and petr. ether) to give III, C₂₀H₂₄N₂, m. 103-4.degree.; HCl salt, m. 221-3.degree. (decompn.)

(MeOH-EtOAc), λ_{max} 3260 Å. (log ϵ 4.30), λ_{min} 2730 Å. (log ϵ 3.61) (alc.); picrate, m. 211-13.degree. (alc.-HCONMe₂). Following the speculation of Boekelheide that highly potent calabash curares might contain a hexahydrobenzindolopyridocoline nucleus the synthesis of various related compds. was undertaken. Excess MeI and the appropriate base kept overnight in C₆H₆ and the ppt. crystd. (MeOH) gave 5,7,8,13,13b,14-hexahydrobenz[g]indolo[2,3-a]pyridocoline methiodide, C₁₉H₁₈N₂.MeI, m. 279.degree. (decompn.), refluxed with excess AgCl in dil. MeOH and recrystd. (MeOH-Me₂CO) to give the corresponding methochloride (XXV), orange-yellow with concd. HNO₃, yellow in concd. H₂SO₄ changed to red with a drop of H₂O and to intense blue-purple with K₂Cr₂O₇; methopicrate, m. 199.degree. (MeOH). XXV had less than 10% activity of d-***tubocurarine***. Attempts to synthesize 8,9-dihydro-14H-benz[h]-

and

6,7-dihydro-12H-benz[f]indolo-[2,3-a]pyridocolinium chlorides from 1-cyanoisoquinoline (XXVI) and 2-cyanoquinoline (XXVII) by the general method failed since the phenylhydrazones of the bromides (XXVIII and XXIX) were recovered unchanged from an attempted Fischer indole reaction. XXVI (2.7 g.) treated with EtO(CH₂)₃MgBr gave 2.2 g. 1-(γ -ethoxybutyryl)isoquinoline, b₂ 170-5.degree.; 2,4-dinitrophenylhydrazone, m. 163.degree. (alc.).

The ketone (1.09 g.) treated with HBr gave 0.8 g. XXVIII, 1,2,3,4-tetrahydro-1-oxobenzo[a]pyridocolinium bromide, C₁₃H₁₂BrNO, m. 223-4.degree. (alc.-Me₂CO), reduced according to Clemmensen to a base, C₁₃H₁₇N; picrate, m. 184.degree. (decompn.). XXVIII (0.8 g.) treated with PhNHNH₂ gave 0.7 g. phenylhydrazone bromide, m. 279.degree. (alc.-Et₂O), converted to the corresponding chloride, C₁₀H₁₈ClN₃.2H₂O, m. 243-6.degree. (alc.-Et₂O), λ_{max} 2430, 2650, 4490, and λ_{min} 2600, 3600 Å. (log ϵ 4.65, 4.06, 4.41, and 4.04, 3.00, in ***acid***), λ_{max} 2300, 2440, 3300, 5120, and λ_{min} 2380, 3020, 3760 Å. (log ϵ 4.38, 4.38, 3.78, 4.44, and 4.36, 3.60, 3.22, in alkali); phenylhydrazone nitrate, m. 237.degree. (alc.); phenylhydrazone picrate, m. 200.degree. (alc.-HCONMe₂). XXVII [2.6 g. prepd. according to Henze (C.A. 31, 57999)] treated with EtO(CH₂)₃MgBr by methods A and B for IV gave, resp., 2.2 g. imine, b_{0.5} 165.degree., ν 3343 cm.⁻¹, and 2 g. 2-(γ -ethoxybutyryl) quinoline, b₂ 190.degree.; 2,4-dinitrophenylhydrazone, m. 148.degree.. The imine or ketone (1.9 g.) refluxed 21 hrs. with AcOH-HBr yielded 1.6 g. XXIX, 1,2,3,4-tetrahydro-4-oxobenzo[c]pyridocolinium bromide, C₁₃H₁₂BrNO.3H₂O, m. 116-18.degree. (MeOH-Me₂CO); phenylhydrazone bromide, m. 251-2.degree. (alc.-Et₂O); phenylhydrazone chloride, m. 257-8.degree. (alc.-Et₂O), λ_{max} 2280, 2680, 3270, 4570, and λ_{min} 2500, 2900, 3670 Å. (log ϵ 4.13, 3.96, 3.62, 4.35, and 3.86, 3.43, 3.24, in ***acid***), λ_{max} 2290, 4890, and λ_{min} 3390 Å. (log ϵ 4.14, 4.27 and 2.97, in alkali); phenylhydrazone nitrate, m. 257-8.degree. (alc.); phenylhydrazone picrate, m. 245.degree. (decompn.) (alc.-Me₂CO).

L10 ANSWER 8 OF 13 CAPLUS COPYRIGHT 2001 ACS

AN 1957:90614 CAPLUS

DN 51:90614

OREF 51:16405d-i,16406a-i,16407a-i,16408a-g

TI Muscarine. V. Indirect proof of the constitution of muscarine by synthetic investigations

AU Eugster, C. H.; Waser, P. G.

CS Univ. Zurich, Switz.

SO Helv. Chim. Acta (1957), 40, 888-906

DT Journal

LA Unavailable

CC 10 (Organic Chemistry)

AB Synthetic investigations into the structure of muscarine, previous to and in support of the formula proposed by Kogl, et al. (C.A. 51, 12058e), are reported, and the syntheses of substituted .beta.-aminotetrahydrofurans and their quaternary salts from .gamma.-lactones, .alpha.-acetylenic ketones, and 3-furancarboxylic acids are described. Me 4,5-dihydro-3-furancarboxylate (28.63 g.) hydrogenated with 1.5 g. 5% Pd-BaSO₄ in MeOH at room temp. and pressure, the mixt. filtered, the filtrate evapd. carefully, and the residue distd. yielded 83% Me tetrahydro-3-furancarboxylate (I), b₁₂ 61-5.degree.. I (18.5 g.) in 30 cc. abs. EtOH treated with 7.1 g. N₂H₄.H₂O, the warm soln. refluxed 1 hr., the solvent evapd., and the residue distd. at 100-10.degree./0.01 mm. gave the hydrazide, m. 85.5-7.0.degree.. The hydrazide in 80 cc. 2N HCl layered with Et₂O, the cooled mixt. stirred with dropwise addn. of 12.1 g. KNO₂ in a small amt. of H₂O, the aq. layer extd. 5 times with Et₂O, the combined exts. and the Et₂O layer cooled by addn. of solid CO₂, the ext. washed with aq. NaCl, dried over MgSO₄, filtered, the filtrate concd. to 1/4 vol., dild. with 50 cc. C₆H₆, evapd. to 1/3 vol., the azide soln. treated with 20 cc. abs. PhCH₂OH, warmed to 40-50.degree. with addn. of Pt tetrahedra, the temp. raised carefully to complete the evolution of N, the mixt. refluxed 3 hrs., the solvent evapd. in vacuo, the residue crystd. from Et₂O, filtered, the mother liquor evapd., and the residue distd. at 120-35.degree./0.02 mm. gave 21.14 g. benzylurethan, m. 60-1.degree. (from petr. ether). The benzylurethan (20.92 g.) hydrogenated with 0.5 g. 5% Pd-BaSO₄ and further addn. of 2 portions of 0.2 g. Pd-C, filtered, the filtrate ***neutralized*** with N HCl, the solvent evapd. in vacuo, the residue taken up in a small amt. of H₂O, the soln. layered with much Et₂O, the H₂O taken up by addn. of sufficient powd. KOH, the Et₂O decanted, the residue extd. several times with boiling Et₂O, the combined exts. dried over KOH, evapd., and the residue distd. gave 6.31 g. .beta.-aminotetrahydrofuran (II), b₅₉ 73.degree., readily sol. in H₂O to a strongly alk. soln. reducing AuCl₃ in 0.1N HCl, Fehling soln., and ammoniacal AgNO₃ on warming, and giving a white ppt. with Nessler reagent. II (4.293 g.), 9.4 g. 35% HCHO, and 6.80 g. 99% HCO₂H heated 10 hrs. at 100.degree., treated with 26 cc. 2N HCl, the soln. evapd. in vacuo, and the residue sublimed at 110-20.degree./0.01 mm. gave 6.212 g. HCl salt, m. 140.degree. (from MeOH-Me₂CO), converted as above to N,N-dimethyltetrahydro-3-furylamine, b₈₀ 77-8.degree.; MeI salt, m. 226.0-6.5.degree. (from EtOH-Et₂O); Me Cl salt (IIa), m. 298-9.degree. (decompn.); MeAuCl₄ salt, m. 228-9.degree. (decompn.). HCO₂Et (85 g.) and 123 g. .gamma.-caprolactone in Et₂O were condensed in the presence of 25 g. Na powder according to Korte and Machleidt (C.A. 50, 16760b), and the crude product was rearranged with MeOH-HCl to an isomeric mixt. of 3-carbomethoxy-5-ethyl-2-methoxytetrahydrofurans, b₁₂₋₁₃ 95-101.degree., cleaved by treatment with 20 drops of concd. H₂SO₄ to 73.07 g. 4-carbomethoxy-2-ethylidihydrofuran, b₁₂₋₁₃ 89-92.degree., .lambda. 254 m.mu. (.vepsiln. 10,000 in EtOH). The ester (71.4 g.) hydrogenated with 5 g. 5% Pd-BaSO₄ in 200 cc. MeOH at room temp. and pressure, the mixt. filtered through Norit-Celite, evapd., the residue reduced in AcOH with 1 g. PtO₂, filtered, and the AcOH carefully evapd. over a glass-ring ***column*** gave 56.3 g. 4-carbomethoxy-2-ethyltetrahydrofuran (III), b₁₃ 87-8.degree.. III (52 g.) and 16.5 g. N₂H₄.H₂O in 80 cc. alc. refluxed 1 hr., treated with 2.0 g. N₂H₄.H₂O, refluxed 1 hr., the solvent evapd. in vacuo, and the product distd. in a high vacuum gave the hydrazide, C₇H₁₄N₂O₂, b_{0.02} 120-30.degree., m. 60.degree. (from CHCl₃-Et₂O and sublimation). The crude hydrazide in 165 cc. 2N HCl was stirred at

0.degree. with 22.7 g. NaNO₂ in 50 cc. H₂O and the mixt. worked up as above. The azide carefully heated with 35.5 PhCH₂OH in 50 cc. C₆H₆ to 45.degree. in 30 min., the temp. raised and, after cessation of N evolution, the mixt. refluxed 2.5 hrs., the solvent evapd., and the residue distd. gave 38 g. benzylurethan, b_{0.1-0.05} 130-40.degree., m. 49.5-50.5.degree. (from Et₂O at -80.degree.), reduced by 2 g. Pd-BaSO₄ in MeOH at room temp. and pressure, with addn. of 400 mg. Pd-C at the end of the reduction. The filtered reduction mixt. dild. with 200 cc. N HCO₂H, evapd. in vacuo, the thick sirup heated 8 hrs. at 100.degree. with 59.3 g. 38% HCHO and 39.8 cc. 98% HCO₂H, the cooled mixt. treated with 76 cc. 2N HCl, evapd. in vacuo, the residue taken up in a small amt. of H₂O, extd. with Et₂O, the aq. soln. made strongly alk. with 50% KOH, exhaustively extd. with CHCl₃, the washed and dried ext. evapd., and the residue distd. through a 10-cm. Vigreux ***column*** gave 11.9 g. 4-amino-2-ethyltetrahydrofuran (IV), b₁₂ 62.5-3.0.degree., quaternized with MeI in Et₂O to the MeI salt, m. 142-4.degree. (from iso-PrOH); MeCl salt (IVa), m. 151-2.degree. (from iso-PrOH-Et₂O); MeAuCl₄ salt, m. 116-18.degree. (from H₂O). Pyranyl propargyl ether (81.5 g.) in 250 cc. dry Et₂O treated dropwise with stirring and cooling (N atm.) in 2 hrs. with BuLi in Et₂O (11.7 mg. Li/cc.), the yellow soln. stirred 2 hrs. at 0.degree., the cooling system removed, the stirring continued until room temp. was reached, the soln. transferred (N atm.) dropwise in 90 min. with stirring to 100 g. pure (EtCO)₂O in 100 cc. dry Et₂O at -80.degree., brought to room temp., kept overnight, externally cooled with ice, cautiously decompd. with H₂O, the Et₂O layer and Et₂O washings of the aq. layer washed with H₂O, NaHCO₃, and NaCl soln., the dried ext. evapd., and the residue distd. gave 58.5 g. 2-hexyn-4-on-1-yl .alpha.-pyranyl ether, b_{0.04} 64-6.degree., .lambda. 218 m.mu. (.epsilon. 7250, EtOH). The acetylene ketone (24.6 g.) in 100 cc. dry Et₂O at -30.degree. treated dropwise with 10 cc. anhyd. NHMe₂, the mixt. kept 14 hrs. at 0-10.degree., evapd., and a sample of the residual oil (29.2 g.) distd. gave 2-dimethylamino-2-hexen-4-on-1-yl .alpha.-pyranyl ether, b_{0.02} 110.degree., .lambda._{max} 322, .lambda._{shoulder} 226, .lambda._{min} 255 m.mu. (log .epsilon. 4.36, 3.29, 2.58, EtOH). The crude ketone (29.2 g.) hydrogenated in AcOH with 1 g. PtO₂, the mixt. filtered, the filtrate evapd., the oily residue taken up in H₂O, extd. with Et₂O, the aq. soln. adjusted to pH 12 with NaOH, exhaustively extd. with Et₂O, the basic residue (14.5 g.) cyclized by heating 1 hr. at 100.degree. with 75 cc. H₃PO₄ (d. 1.7) and 230 cc. H₂O, the cooled soln. steam-distd., the distillate ***neutralized*** with HCl, the soln. evapd. in vacuo, the residue taken up in a small amt. of H₂O, the soln. adjusted to pH 14 with KOH, extd. with Et₂O, the dried ext. evapd. and the residue distd., gave 6 g. oily IV. Similarly [MeCH(OMe)-CO]₂O, b₁₀ 97-9.degree., .nu. 1757, 1835 cm.⁻¹, was converted through the methoxylated acetylene ketone, C₁₄H₂₅O₄, b_{0.05} 100.degree., .lambda. 221 m.mu. (.epsilon. 5050, EtOH), to the amino ketone, C₁₄H₂₅NO₄, b_{0.02} 140-5.degree., .lambda. 322 m.mu. (.epsilon. 22750, EtOH), reduced with LiAlH₄ to the unsatd. amino alc., C₁₄H₂₇NO₄, b_{0.02} 110-15.degree., .lambda. 234 m.mu. (log .epsilon. 3.58, EtOH), and further reduced with 5% Pd-BaSO₄ in EtOH to the satd. amino alc., b_{0.04} 80-100.degree.. The cyclization of this isomeric mixt. was unsatisfactory. 3-Furoic ***acid*** (75.5 g.) (prepd. by decarboxylation of furantetra-carboxylic ***acid*** according to Smith, et al., C.A. 46, 4338f) in 83 cc. abs. MeOH and 208 cc. (CH₂Cl)₂ boiled 15 hrs. with 1.97 cc. concd. H₂SO₄, treated with 20 cc. MeOH and 0.5 cc. concd. H₂SO₄, boiled 2 hrs., the cooled soln. dild. with the same vol. of Et₂O, extd. with aq. NaHCO₃, and the org. layer dried and carefully evapd. gave 68.13 g. Me 3-furoate, b₄₂ 78-80.degree.. The ester

(51.9 g.) and 45 cc. Ac₂O at 50.degree. treated with 5.5 g. BF₃-Et₂O complex, the soln. heated in 5 min. to 95.degree., the heating stopped, the mixt. at 60.degree. cooled externally with ice, the cold mixt. decompd. with H₂O and excess Et₂O, the Et₂O soln. washed with H₂O and Na-HCO₃, dried, evapd., and the residue distd. gave 31.27 g. Me 5-acetyl-3-furoate (V), b₁₁ 115-30.degree. (pure product, b₁₁ 128-9.degree.), m. 88.5-9.0.degree. (from Me₂CO-petr. ether), .lambda. 263 m.mu. (.epsilon. 13,240, alc.); p-nitrophenylhydrazone, m. 238.5-9.5.degree.. Sublimed 3-furoic ***acid*** (36.81 g.) heated to 60.degree. in 40 cc. Ac₂O, treated with 4 cc. BF₃-Et₂O, quickly heated to and maintained 15 min. at 125.degree., the cooled mixt. shaken with 20 cc. 2N AcOH, evapd. in vacuo, the residue taken up in H₂O, treated with Norit, filtered hot, the filtrate dild. with an equal vol. of Me₂CO, filtered through 120 g. Al₂O₃ (Woelm, ***acid***), the ***column*** washed with 1 l. 1:1 Me₂CO-H₂O, the combined eluates evapd. in vacuo, the mixt. sublimed at 0.02 mm., and the crude product crystd. from H₂O gave 17.5 g. 5-acetyl-3-furoic ***acid*** (Va), m. 208.0-9.5.degree., .lambda.max. 205, 265, .lambda.min. 219 m.mu. (.epsilon. 13,600, 12,720, 2100, EtOH). Va (500 mg.) in 10 cc. ice-cold 2N NaOH treated dropwise with 850 cc. 0.1N KMNO₄ until the violet color persisted 5 min., the soln. heated, filtered, the filtrate evapd. in vacuo, the residue taken up in a small amt. of H₂O, the soln. extd. with Et₂O, the aq. soln. acidified, extd. exhaustively with Et₂O, the ext. evapd., the residue sublimed, the sublimate crystd. from H₂O, and the cryst. product sublimed gave 20 mg. 2,4-furandicarboxylic ***acid***, m. 268.degree., .lambda.max. 240, .lambda.min. 215 m.mu. (log .epsilon. 4.02, 3.67, H₂O). V (31.19 g.) in 200 cc. 1:1 EtOH-EtOAc reduced with 5 g. 5% Pd-BaSO₄, the mixt. filtered through a layer of Celite, the filtrate evapd. in vacuo, the residue in 150 cc. MeOH completely reduced in 2 hrs. with 3 g. prerduced PtO₂ in 50 cc. AcOH, the mixt. filtered, the filtrate evapd. in vacuo, and the residue distd. gave 29.65 g. Me 5-(.alpha.-hydroxyethyl)tetrahydro-3-furancarboxylate (VI), b₁₀ 130-6.degree.. VI (27.5 g.) in 50 cc. abs. alc. treated with 8.00 g. N₂H₄.H₂O, the mixt. refluxed 1 hr., evapd., the crude hydrazide taken up in 76 cc. 2.28N HCl, dild. with 50 cc. Et₂O, the ice-cold mixt. stirred with dropwise addn. of concd. aq. NaNO₂ (12.0 g.), adjusted to pH 1.0 with HCl, the Et₂O layer cooled with solid CO₂, the aq. layer extd. 7 times with 60 cc Et₂O, the combined dry exts. evapd. to 1/4 vol., treated with 100 cc. C₆H₆, the mixt. evapd. to 1/3 vol., dild. with C₆H₆, reevapd., the clear yellow azide soln. slowly heated on a steam bath with 50 cc. freshly distd. PhCH₂OH, finally refluxed 6 hrs., the solvent and PhCH₂OH evapd. in vacuo, and the residue distd. gave 15-60 g. benzylurethan, b_{0.04} 155-65.degree., which was hydrogenated with 2 g. 5% Pd-BaSO₄ and 500 mg. Pd-C, the mixt. filtered, the filtrate evapd., the residue taken up with ice cooling in 11.1 g. 38% HCHO and 13.5 g. 98% HCO₂H, the soln. refluxed 6 hrs., the cooled mixt. concd., the concentrate treated with excess 40% KOH, extd. with CHCl₃, the dried ext. evapd., and the residue distd., giving 6.35 g. N,N-dimethyl-2-(.alpha.-hydroxyethyl)tetrahydro-4-furylamine (VII), b. 110-15.degree.; picrate, m. 109-13.degree. (from alc.). VII (2.50 g.) in 20 cc. Et₂O treated with 2 cc. MeI, refluxed several hrs., and the oily product triturated with Me₂CO gave the cryst. MeI salt, m. 137-47.degree., converted with AgCl into the hygroscopic chloride, which, dried in a high vacuum and crystd. from iso-PrOH-Me₂CO, yielded an isomeric mixt. of VII MeCl salts, m. 149-51.degree.; the mixt. (3.847 g.) in a min. of solvent 16 (cf. C.A. 51, 355i) ***chromatographed*** on 1.47 kg. cellulose powder pre-washed with solvent 16, the ***column*** eluted with the same solvent to give 300 fractions of 1000 drops, fractions 122-37 and 157-270 combined,

evapd., the residue taken up in H₂O, acidified with HCl, the ***acid*** solns. clarified with Norit, evapd., the residues taken up in abs. alc., filtered, the filtrates, evapd., and the residues crystd. from iso-PrOHMe₂-CO gave isomer (VIIA.MeCl), m. 140-2.degree. (MeBPh₄ salt, m. 214.5-16.5.degree.; MeAuCl₄ salt, m. 114.5-15.0.degree.; reineckate, m. 145-6.degree.), and isomer (VIIB.MeCl), m. 175.5-6.0.degree. (Me-BPh₄ salt, m. 196.0-6.5.degree.; MeAuCl₄ salt, m. 151.0-2.5.degree.). Va (2.140 g.) heated 1.5 hrs. with 5 cc. pure SOCl₂ at 110.degree., the excess SOCl₂ evapd., and the residue distd. gave 950 mg. ***acid*** chloride, converted by treatment in 5 cc. Et₂O at 0.degree. with 1.2 g. NaN₃ in H₂O to the cryst. azide, ***purified*** by taking up in CHCl₃ or Me₂CO, sepg. the H₂O layer, filtering, and evapg. in vacuo. The pure cryst. azide treated with 5 cc. 98-9% HCO₂H, carefully heated in the presence of Pt tetrahedra to 80-5.degree., maintained 1 hr., heated 10 min. to 100.degree., the soln. evapd. in vacuo, the residues taken up in hot H₂O, decolorized with Norit, filtered hot, the cooled soln. filtered, and the almost colorless cryst. residue sublimed at 130-50.degree./0.04 mm. gave 292 mg. pure 5-acetyl-3-formamidofuran (VIII), m. 190-1.degree., .lambda.max. 229, 295, .lambda.min. 263 m.mu. (.epsilon. 14,900, 8160, 2730, alc.). VIII (20.2 mg.) hydrogenated 165 min. with 9.34 cc. H in 5.00 cc. MeOH in the presence of 20.3 mg. brown Pd oxyhydrate-BaSO₄ (cf. Kuhn and Haas, C.A. 50, 3675d) and the product distd. gave 3-formamido-5-(.alpha.-hydroxyethyl)tetrahydrofuran (IX), b_{0.02} 100-20.degree.. IX (150 mg.) in ice-cold tetrahydrofuran added dropwise to 210 mg. Li-AlH₄ in 5 cc. Et₂O, the mixt. refluxed, kept 14 hrs. at room temp., decompd. with H₂O, filtered through Celite, the filtrate evapd., and the residue distd. gave 140 mg. 5-(.alpha.-hydroxyethyl)-3-(methylamino)tetrahydrofuran (X), b_{0.08} 90-100.degree., quaternized in alc. with 0.2 cc. MeI and 1.0 cc. N KOH by boiling 1 hr., acidifying with HCl, evapg. in vacuo, extg. the residue with alc., filtering, and evapg. to give 162 mg. mixt. of VIIA.- and VIIB.MeCl. VIIA.MeCl (42.8 mg.) in 5.00 cc. H₂O oxidized 26 min. with 80 mg. PtO₂, the mixt. filtered, the filtrate evapd., and the residue crystd. from iso-PrOH-Et₂O gave trimethyl(2-acetyl-4-tetrahydrofuryl)ammonium chloride (XI), m. 186-9.degree., also obtained by oxidation of VIIB.MeCl, ***purified*** by recrystn. of the mixed XI from iso-PrOH-Et₂O and drying at 100.degree./0.02 mm. to give XI, C₉H₁₈ClNO₂.1/3H₂O, m. 185.5-7.0.degree., .nu. 1709 cm.⁻¹ (Nujol); MeAuCl₄ salt, m. 119-20.degree. (from H₂O), .nu. 1709 cm.⁻¹ (Nujol). Pure muscarine chloride (XII) (19.3 mg.) (from I. patouillard) in 5.00 cc. H₂O oxidized 12 hrs. with 40 mg. prerduced PtO₂, the mixt. filtered, and the filtrate boiled 1 hr. with 200 mg. Ag₂O in the app. of Wiesenberger (C.A. 41, 3017d) gave a distillate ***neutralized*** by less than 0.2 cc. 0.05N HCl (methyl red). XII (19.6 mg.) similarly oxidized 14 hrs. with 100 mg. PtO₂ in 0.1N AcOH, the mixt. filtered, the filtrate evapd. in vacuo, the residue taken up in ice-cold H₂O, treated with excess H₂AuCl₄, filtered, and the residue dried in a high vacuum gave oxomuscarine tetrachloroaurate, m. 89-93.degree., .nu. 1752 cm.⁻¹ (Nujol). Oxomuscarine chloride (XIII), [.alpha.]D₂₄ 3.9.degree. (c 5.08, alc.), .lambda. 279 m.mu. (.epsilon. 139, H₂O), .nu. 1754 cm.⁻¹, R_f in solvents 14 and 16 similar to those of XII, giving a red color with Dragendorff reagent, reducing H₂AuCl₄ in the presence of alkali and Fehling soln. on heating, and giving no reaction with triphenyltetrazolium chloride and Schiff reagent. XIII reduced with KBH₄ in MeOH, decompd. with HCl, the mixt. evapd. in vacuo, and the residue extd. with alc. gave a product with R_f 0.24 in solvent 16 (XII, VIIA.MeCl, VIIB.MeCl showed R_f 0.25, 0.20, 0.16, resp.). trans-Trimethyl(2-hydroxycyclopentyl)ammonium chloride (790 mg.) [from the iodide with AgCl

(cf. Friess and Baldridge, C.A. 50, 16926h)] in 5.00 cc. H₂O oxidized 14 hrs. with Pt from 1.00 g. PtO₂, and the mixt. worked up gave the unstable quaternary oxo chloride, converted into the more stable tetrachloroaurate, m. 160-70.degree. (decompn. with cleavage of NMe₃) (from alc.), .nu. 1751 cm.⁻¹ (Nujol). The infrared spectrum of XIII indicated the presence of a 5-membered ring. The behavior of XIII in the presence of alkali showed that the NMe₃ group is not in the .alpha.- or .beta.-position to the CO group and accordingly I has the structure proposed by Kogl, et al. (loc. cit.). The pharmacol. testing of IIa, IVa, VIIA.MeCl, and VIIB.MeCl on frog and cat preps, showed nicotine- and ***curare*** - but less muscarinelike activity than that of I.

L10 ANSWER 9 OF 13 CAPLUS COPYRIGHT 2001 ACS

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DN 51:81536

OREF 51:14759i,14760a-i,14761a-i,14762a-h

TI Constitution of athamantin and oroselol

AU Halpern, O.; Waser, P.; Schmid, H.

CS Univ. Zurich, Switz.

SO Helv. Chim. Acta (1957), 40, 758-78

DT Journal

LA Unavailable

CC 10 (Organic Chemistry)

GI For diagram(s), see printed CA Issue.

AB Exptl. proof was sought for the clarification of the doubtful structure of athamantin (I) (cf. Spath and S., C.A. 35, 47526). Dry I (300 mg.) in 10 ml. N NaOMe kept 22 hrs. at 4-10.degree., the yellow soln. satd. with CO₂, the solid mixt. dild. with CO₂-satd. H₂O and satd. with CO₂, the cloudy mixt. repeatedly ext. with Et₂O-C₅H₁₂, the org. ext. washed with H₂O, 2:1 satd. NaHCO₃-Na₂CO₃, and aq. NaCl soln., the dried ext. evapd. and the cryst. residue (229.4 g.) ***chromatographed*** on a 20-fold amt. of neutral Al₂O₃ (dried at 110.degree. and treated with 5% H₂O), eluted with 1:1 C₆H₆-C₅H₁₂, and the fraction recrystd. from C₅H₁₂-Et₂O or C₅H₁₂-C₆H₆ gave 123 mg. compd. A (II), m. 104-5.degree., [.alpha.]_D²⁰ 0.00 +- 0.02.degree. (c 1.2, MeOH), .lambda. (max.) 218, 249, 257, 285, 293 (shoulder), (min.) 234, 253, 269 m.mu. (log .epsilon. 4.52, 4.18, 4.22, 3.51, 3.46, 3.81, 4.13, 3.30, in 96% alc.), intense blue in Gibbs test, colorless soln. in dil. NaOH. Dry I (600 mg.) refluxed 3 hrs. in 15 ml. N NaOMe (dry atm.), the intense yellow soln. ***neutralized*** with excess AcOH at 0.degree. and evapd. in vacuo, the residue taken up in H₂O, the soln. kept 30 min.-1 hr. and shaken out with Et₂O, the Et₂O ext. extd. 5 times with 3-ml. portions 1:1 satd. NaHCO₃-Na₂CO₃ solns. and exhaustively with ice-cold 0.5% aq. KOH, the alk. exts. acidified to pH 5 [ext. P (III)], the Et₂O ext. washed with aq. NaCl, the dried ext. evapd., and the cryst. residue (61.5 mg.) distd. at 150-60.degree./0.02 mm. and recrystd. from C₅H₁₂-Et₂O and C₅H₂-C₆H₆ gave furocoumarin C (IV), m. 116-17.degree., .lambda. (max.) 215, 251, 301, (min.) 230, 272 m.mu. (log .epsilon. 4.22, 4.48, 4.06; 4.00, 3.64) [2,4-dinitrophenylhydrazine deriv. (IVa), m. 208-10.degree. (from EtOAc)], blue-green Gibbs test, oxidized with CrO₃ to AcOH only (cf. C.A. 48, 10491g; 50, 4986b), pos. lactone ring test. III satd. with NaCl and extd. with Et₂O, the ext. washed with NaHCO₃ and NaCl solns., the dried ext. evapd., the cryst. residue (273 mg.) taken up in 3:1 C₆H₆-Et₂O and filtered through 1 g. washed silica gel, and the evapd. eluate recrystd. from Et₂O-petr. ether and C₆H₆-petr. ether gave 130 mg. 2-(1-methyl-1-methoxyethyl)-4-hydroxy-5-(2-carbomethoxyvinyl)benzofuran (V), m. 156-7.degree., .lambda. (max.) 224, 251, 296, 334, (min.) 230, 274, 328 (log .epsilon. 4.11, 4.49, 4.23, 3.90,

4.09, 3.95, 3.89), yellow soln. in 0.5% KOH, no FeCl_3 reaction, blue-green Gibbs reaction, giving only AcOH on CrO_3 microoxidation. I (800 mg.) boiled 3 hrs. with 20 ml. N NaOMe, the mixt. satd. with CO_2 and dild. with H_2O satd. with CO_2 , the mixt. satd. with CO_2 and extd. with Et_2O , the ext. shaken with aq. NaHCO_3 (the alk. ext. combined with the aq. phase), the Et_2O ext. exhaustively extd. with ice-cold 0.5% KOH (the alk. ext. satd. with CO_2 to give 283 mg. pure V), and the Et_2O ext. evapd. gave a trace of IV and $\text{Me}_2\text{CHCH}_2\text{CO}_2\text{Me}$. The aq. phase acidified to Congo red and extd. 2 hrs. with Et_2O , the ext. worked up, and the product distd. in high vacuum yielded 71 mg. IV, ***purified*** by ***chromatography*** in 1:1 C_6H_6 -petr. ether over 3 g. neutral Al_2O_3 and recrystd. from C_5H_{12} and C_6H_6 - C_5H_{12} . II (25 mg.) boiled 2.75 hrs. in 2 ml. N NaOMe and the mixt. worked up as above produced a 0.5% KOH ext. yielding V, and a neutral fraction giving IV. IV (39.8 mg.) treated with 3 ml. boiling N NaOMe yielded 11.4 mg. V from the phenolic reaction product. V was converted into the acetate, m. 123.5-4.5.degree. (from Me_2CO - H_2O and MeOH - H_2O); Me ether (Va), m. 107.5-8.5.degree. (from Et_2O -petr. ether), no Gibbs color reaction; 2,4-dinitrophenylhydrazine deriv., m. 195.5-6.5.degree. (decompn.), λ_{max} 251, 299, 344, (shoulder) 430, (min.) 224, 276, 318 (log ϵ 4.50, 4.25, 4.27, 3.38, 4.13, 4.11, 4.16). V (50 mg.) kept 18 hrs. at 10.degree. in 1.6 ml. 5% aq. KOH, the soln. satd. with CO_2 , acidified with AcOH, and filtered, and the ppt. crystd. from Me_2CO -petr. ether and Me_2CO (or C_6H_6) gave a compd. m. above 310.degree., blue-green Gibbs test. V (50.00 mg.) in 5 ml. AcOH hydrogenated with 3.04 moles H in 5.5 hrs. at 17.degree./716 mm. in the presence of 15.5 mg. 30% Pd-norite catalyst, the mixt. filtered, the filtrate evapd., the residue kept overnight in excess 2.5% KOH in dil. MeOH, the with H_2O , the MeOH evapd. in vacuo, the aq. soln. acidified to Congo red and extd. with Et_2O , the ext. worked up, the product distd. at 130-40.degree./0.02 mm., and the cryst. portion of the distillate crystd. from dil. MeOH gave the known hexahydroorselone, m. 98.degree.. V (30 mg.) in a little abs. CHCl_3 ozonized with 1.7 l. 1% O_3 in O at 0.degree., the CHCl_3 evapd. in vacuo, the residue treated with dil. aq. NaCl, the soln. distd. at 100-10.degree. in N into dil. p- $\text{O}_2\text{NC}_6\text{H}_4\text{NHNH}_2\cdot\text{HCl}$, the ppt. (4 mg.) sublimed at 130.degree. in high vacuum, and the sublimate recrystd. from dil. alc. gave acetone p-nitrophenylhydrazone, m. 144-5.degree.. The remaining distillate steam-distd. gave 8 mg. needles, sublimed at 65-70.degree./0.02 mm. and crystd. from dil. Me_2CO to give resorcinol-2,4-dialdehyde, m. 128.0-8.5.degree.. V (10 mg.) ozonized in CHCl_3 at -15.degree. or -80.degree., the CHCl_3 evapd. and the residue steam-distd. (N atm.), the ***acid*** distillate made alk. with a few drops of aq. KOH and paper-***chromatographed*** in BuOH- H_2O - NH_2Et gave, in both expts., spots corresponding to AcOH and $\text{Me}_2\text{C}(\text{OMe})\text{CO}_2\text{H}$. Oroselone (VI) (50 mg.) in 2 ml. CHCl_3 and 1 ml. AcOH ozonized at 0.degree. with 3 l. 2% O_3 -O, the CHCl_3 evapd. at 20.degree. in vacuo, the residue steam-distd., the distillate treated with p- $\text{O}_2\text{NC}_6\text{H}_4\text{NHNH}_2$, and the ppt. sublimed gave formaldehyde p-nitrophenylhydrazone, m. 180-1.degree. (from dil. alc.). V (20 mg.) in 5 ml. alc. illuminated 6 hrs. with unfiltered ultraviolet light, the soln. evapd. in vacuo and the product freed from small amts. of phenolic by-products gave IX for which an α -pyrone ring structure was proposed. I (120 mg.) heated 4 hrs. at 100.degree. with 5 ml. N NaOMe, the soln. treated portionwise at 100.degree. in 45 min. with 1.2 ml. Me_2SO_4 in 15 ml. NaOMe under const. alk. conditions, kept 30 min. at 100.degree., cooled, ***neutralized*** at 0.degree. with AcOH, and evapd. at 30.degree. in vacuo, the residue taken up in H_2O and extd. with Et_2O , the washed and dried ext. evapd., the residue ***chromatographed*** over 1.3 g. neutral Al_2O_3 and eluted with 3:1

petr. ether -C₆H₆, and the product crystd. from Et₂O-petr. ether gave Va. I (400 mg.) in 5 ml. pure dioxane stirred with 8 ml. 5% aq. NaOH, the soln. kept 20 hrs. at 20.degree. and acidified to weak Congo red, the ***acid*** soln. kept at 0.degree. several days and filtered, and the crude product treated with Norit in Me₂CO and recrystd. repeatedly from Me₂CO-H₂O and Me₂CO-Et₂O gave an amorphous, optically inactive bimol. compd., C₂₈H₂₂O₇, .lambda. (max.) 254, 302, (min.) 233, 279 m.mu. (log .epsilon. 4.67, 4.33, 4.37, 4.12). I (200 mg.) in 6 ml. AcOH hydrogenated 18 hrs. with 1.9 moles H in the presence of 170 mg. PdO₂, the soln. evapd. at 40.degree. in vacuo, the product, [.alpha.]D₁₅ 37.5.degree. (AcOH), heated 3.5 hrs. at 100.degree. with 5 ml. 5% KOH, acidified, and extd. with Et₂O, the ext. washed with aq. NaCl and evapd., the residue distd. at 160-80.degree./0.05 mm., and the oily residue recrystd. from Et₂O-petr. ether yielded 70 mg. VII, m. 112-13.degree., [.alpha.]₅₈₉₁₉ 86.7 .+- .2.degree., [.alpha.]₅₄₆₂₂ 106.2 .+- .2.degree., [.alpha.]₄₃₆₂₁ 129.1 .+- .6.degree. (c 0.6504, MeOH), [.alpha.]₅₈₉₁₉ 66.5 .+- .2.degree., [.alpha.]₅₄₆₂₀ 82.2 .+- .2.degree., [.alpha.]₄₃₆₂₁ 100.6 .+- .6.degree. (c 0.620, CHCl₃), .lambda. (max.) 280, 289, (min.) 261, 285 m.mu. (log .epsilon. 3.30, 3.32, 2.88, 3.31); acetate, [.alpha.]D₂₀ 58.5 .+- .1.5.degree. (c 0.729, CHCl₃). VII (17 mg.) in 3 ml. H₂O distd. slowly (N atm.) with 0.5 ml. mixt. (6 g. K₂Cr₂O₇ and 8 g. H₂SO₄ in 27 ml. H₂O) into dil. aq. p-O₂NC₆H₄NHNH₂.HCl, the ppt. (5 mg.) sublimed, the sublimate crystd. from dil. alc. and Et₂O-petr. ether gave acetone p-nitrophenylhydrazone, m. 146-8.degree.. I (5 g.) in 50 ml. Et₂O added dropwise in 2-3 hrs. at 20.degree. to vigorously agitated 2.5 g. LiAlH₄ in 200 ml. abs. Et₂O, the mixt. stirred 4 hrs., kept overnight, treated cautiously with EtOAc-Et₂O, ***neutralized*** with cold N HCl, and extd. with CH₂Cl₂, the dried ext. evapd. in vacuo, the residue taken up in a little MeOH and kept 12 hrs. with excess CH₂N₂ in Et₂O, the mixt. worked up, the residue extd. with C₅H₁₂, and the insol. product ***chromatographed*** over 100 g. Al₂O₃ (contg. 10% H₂O), eluted with 400 ml. C₆H₆ and 1200 ml. 20:1 and 10:1 C₆H₆-CH₂Cl₂ and the product crystd. repeatedly from Et₂O gave 2-(1-methyl-1-hydroxyethyl)-2,3-dihydro-4-methoxy-5-[2-(hydroxymethyl)vinyl] benzofuran (VIII), C₁₅H₂₀O₄, m. 95-6.degree., [.alpha.]D₂₁ 57.4 .+- .2.degree. (c 0.714, CHCl₃), .lambda. (max.) 217, 261, (min.) 238 m.mu. (log .epsilon. 4.39, 4.17, 3.81). Further elution with CH₂Cl₂-MeOH gave the amorphous 3-HO deriv. (IX) of VIII, [.alpha.]D₁₇ 59 .+- .3.degree. (c 1.00, MeOH), .lambda. (max.) 260, (min.) 244 m.mu. (log .epsilon. 3.8, 3.63). The formation of VIII and IX was only possible if I had the proposed formula. I, [.alpha.]₅₈₉₂₁ 102.3 .+- .2.degree., [.alpha.]₅₄₆₂₂ 129.0 .+- .2.degree., [.alpha.]₄₃₆₂₂ 161.4 .+- .6.degree. (c 0.5575, MeOH), [.alpha.]₅₈₉₂₁ 60.0 .+- .1.degree., [.alpha.]₅₄₆₂₁ 73.9 .+- .1.degree., [.alpha.]₄₃₆₂₁ 86.3 .+- .3.degree. (c 1.024, CHCl₃). In AcOH the rotation of I, [.alpha.]D₂₀ 88 .+- .1.degree. (c 1.145), remained const. during several days, but I (c 0.465, N p-MeC₆H₄SO₃H in MeOH) at 20 .+- .2.degree. had .alpha._D 0.51, 0.66, 0.64, 0.56, 0.04.degree. in 1, 17, 41, 89, and 1152 hrs., resp., and had decompd. to a mixt. of VI and a substance with the ultraviolet absorption spectrum of IV. I also racemized in N HCl in MeOH with formation of VI which was itself partially changed under these conditions. Et₂O ext. (4.5 g., from roots of Athamanta oroselinum) ***chromatographed*** on 225 g. 3:1 ZnCO₃-Hyflo, eluted with C₅H₁₂ and 3:1 C₅H₁₂-C₆H₆ to remove oils, VI, and I, eluted further with C₅H₁₂-C₆H₆-Et₂O, and the product crystd. from Et₂O or CH₂Cl₂ and ***purified*** by high vacuum distn. gave optically inactive oroselol (X), m. 156-7.degree., .lambda. (max.) 251, 301, (min.) 230, 272 m.mu. (log .epsilon. 4.44, 4.04, 3.64), oxidized by CrO₃ to give Me₂CO, no MeO group, no FeCl₃ or Gibbs reactions.

X (40 mg.) heated 30 min. at 100.degree. with 1 ml. MeOH and 0.5 ml. concd. HCl, the mixt. dild. with H₂O, and the ppt. ***purified*** by high vacuum distn. and crystn. from Et₂O and EtOH gave VI, also obtained by refluxing X 2.5 hrs. with NaOAc-Ac₂O. X (10 mg.) in 3 ml. 0.9N HCl in abs. MeOH kept 24 hrs. at 20.degree., the mixt. poured into excess aq. NaHCO₃ and extd. with CH₂Cl₂-petr. ether, the ext. evapd., the residue distd. at 140-50.degree. in high vacuum, the crude product (m. 107-10.degree.) taken up in C₆H₆ and filtered through ZnCO₃-Hyflo, the filtrate evapd., and the residue crystd. from C₆H₁₂ or Et₂O gave IV. The transformation of X to IV and VI permitted the assignment of a coumarin formulation. The coumarin-coumaric ester reversible rearrangement was investigated. Umbelliferone Me ether (XI) (800 mg.) refluxed 3.5 hrs. with 40 ml. N NaOMe, the mixt. satd. with CO₂, dild. with H₂O, again satd. with CO₂, evapd. in vacuo at 30.degree., and extd. with Et₂O, the Et₂O ext. shaken out with ice-cold 0.5% aq. KOH, the aq. ext. acidified and, after long standing, filtered, and the residue (540 mg.) recrystd. from C₆H₆-petr. ether gave Me trans-2-hydroxy-4-methoxycinnamate (XII), m. 144.5-5.0.degree., yellow soln. in NaOH, blue-green Gibbs test, not converted to XI on brief distn. at normal pressure; free ***acid***, m. 195-8.degree. (from H₂O). XI (500 mg.) kept 20-24 hrs. at 4-6.degree., the mixt. satd. with CO₂, dild. with H₂O in a strong stream of CO₂, evapd. in vacuo at 20-30.degree., and extd. with Et₂O, and the Et₂O extd. with 0.5% aq. KOH, the alk. ext. acidified and extd. with Et₂O, and the product on evapn. recrystd. from Et₂O-petr. ether and dil. MeOH gave 380-400 mg. Me .beta.-methoxy-.beta.-(2-hydroxy-4-methoxyphenyl)propionate (XIII), m. 83.5-4.5.degree., colorless soln. in NaOH, blue Gibbs test, converted by distn. at 160.degree./14 mm. to XI. XIII (60 mg.) heated 15 min. at 100.degree. with 0.3 ml. AcOH, the mixt. evapd. in vacuo and worked up as above gave 2.2 mg. crude XI and 50 mg. phenolic material ***purified*** by filtration in Et₂O through neutral Al₂O₃ and crystn. of the product from C₆H₆-petr. ether to give XII. XIII (200 mg.) methylated 10 hrs. at 60-5.degree. with K₂CO₃ and MeI in Me₂CO, the mixt. worked up, and the 178 mg. cryst. neutral product recrystd. from Et₂O-petr. ether gave Me .beta.-methoxy-.beta.-(2,4-dimethoxyphenyl) propionate (XIIIa), m. 52.5-5.0.degree., .lambda. (max.) 228, 276, (min.) 249 m.mu. (log .epsilon. 3.94, 3.47, 2.54) (similar to that of XIII), distd. unchanged at 180-200.degree./14 mm. XIIIa (65 mg.) heated 3 hrs. at 100.degree. with 3 ml. N NaOMe, the mixt. worked up, and the crude product (m. 83.5-5.0.degree.) distd. at 120.degree./0.03 mm. and recrystd. from Et₂O-petr. ether gave the known Me trans-2,4-dimethoxycinnamate, m. 86.5-7.0.degree.. XI (100 mg.) was heated 3 hrs. at 85 +/- 2.degree. (anhyd. atm.) with 5 ml. N NaOMe, the cooled mixt. ***neutralized*** with AcOH, evapd. at 20.degree. in vacuo, dild. with H₂O, and extd. with Et₂O, the Et₂O ext. shaken with aq. NaHCO₃ (ext. A), and exhaustively extd. with ice-cold 0.5% KOH (ext. B). Acidification of ext. A yielded 18.9 mg. XI. Ext. B satd. with CO₂ and worked up gave 70.3 mg. XII. Evapn. of the original Et₂O ext. gave 14.2 mg. XI. By similar treatment, 100 mg. XII produced 11.2 mg. XI and 90.6 mg. XII; 100 mg. XIII gave 22.7 mg. XI and 46 mg. XII. .beta.-Methoxymeliotic esters of type XIII constituted the intermediate products in the alkylate catalyzed reversible coumarin (or coumarinic ester)-coumaric ester rearrangement. I had a 100 times stronger coronary dilating activity than aminophyllin and a 10-fold weaker spasmolytic activity on the ***isolated*** intestine than ***papaverine***. In the mouse the toxicity of I was equiv. to that of khellin and ***papaverine***.

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 TI Synthesis of alicyclic derivatives structurally related to morphine. II
 AU Winternitz, F.; Antia, N. J.; Tumlirova, M.; Lachazette, R.
 CS Univ. Montpellier
 SO Bull. soc. chim. France (1956) 1817-28
 DT Journal
 LA Unavailable
 CC 10 (Organic Chemistry)
 AB cf. C.A. 47, 4295e. The importance of the O bridge in ***morphine*** analogs for physiol. activity may be relative to the completeness of the structural analogy. With lack of phenanthrene or isoquinoline components, the necessity for the furan structure for ***morphine*** -like activity may become more evident as shown by the synthesis of such compds. from 2-phenoxy cyclohexanone (I). Anhyd. K₂CO₃ (132 g.), 127 g. 2-chlorocyclohexanone, 90 g. redistd. PhOH, and 150 cc. Me₂CO refluxed 6 hrs., cooled and filtered, the filtrate and Me₂CO washings evapd., the residue taken up in Et₂O, the washed and dried ext. evapd. and the product recrystd. from Et₂O-petr. ether gave 100 g. I, m. 63-4.degree.; dinitrophenylhydrazone, m. 145-6.degree. (from alc.). I (5 g.) added portionwise with stirring to 50 cc. H₃PO₄, the mixt. heated 2 hrs. at 100.degree., cooled and poured onto cracked ice, the mixt. extd. with Et₂O, the washed and dried ext. evapd. and the residue distd. in vacuo gave 3.3 g. tetrahydrodibenzofuran (II), b_{0.02} 100-10.degree.; picrate, m. 97-8.degree. (from alc.), converted by ***chromatography*** in C₆H₆ over Al₂O₃, to a compd., C₁₂H₁₂O, b_{0.02} 90-2.degree. II (2 g.) in 25 cc. CCl₄ brominated with 2 g. N-bromosuccinimide under 120-w. illumination, the mixt. cooled to 0.degree. and filtered, the filtrate evapd. in vacuo and the residue (3 g.) refluxed 8 hrs. with 2 g. anhyd. K₂CO₃ in 20 cc. dioxane, the mixt. cooled and taken up in H₂O, the soln. extd. with Et₂O and the residue on evapn. distd. in vacuo gave 0.5 g. dihydrodibenzofuran (III), b_{0.02} 95-7.degree., λ . 250, 280, 286, 296 m. μ . (log ϵ . 4.08, 3.82, 3.79, 3.40) (picrate, m. 95.0-6.5.degree.), together with viscous oily bromotetrahydrodibenzofuran (IV), b_{0.02} 115-20.degree.. III (0.2 g.) heated 2 hrs. at 300.degree. with 0.2 g. 25% Pd-C and the product extd. with Et₂O gave, on standing, cryst. dibenzofuran, m. 82-3.degree. (from alc.); picrate, m. 95-7.degree.. IV (7.7 g.) in 25 cc. anhyd. C₆H₆ and 20 cc. 30% NHMe₂ in C₆H₆ were kept at room temp. 24 hrs., the mixt. poured onto ice, the C₆H₆ layer washed with 10% HCl, the washing and the aq. layer made alk. with Na₂CO₃ and extd. with Et₂O, the washed and dried ext. evapd. and the residue distd. in vacuo yielded 71% dimethylamino-1,2,3,4-tetrahydrodibenzofuran (V), b_{0.04} 90-8.degree.; HCl salt, m. 244-6.degree. (from alc.-Et₂O); picrate, m. 164-5.degree.. PhSH (4 g.), 5 g. 2-chlorohexanone, and 5 g. K₂CO₃ in 40 cc. Me₂CO refluxed 15 hrs., cooled and taken up in H₂O, extd. with Et₂O, the washed and dried ext. evapd. and the residue distd. in vacuo yielded 81% 2-(phenylthio)cyclohexanone (VI), b_{0.04} 118-20.degree., m. 53-4.degree. (from Et₂O-petr. ether); 2,4-dinitrophenylhydrazone, m. 158-60.degree.. VI (10 g.) in 50 cc. AcOH and 33 cc. Ac₂O treated portionwise with 56 cc. 30% H₂O, the mixt. heated 2 hrs. at 80.degree. and concd. in vacuo after destruction of excess H₂O, the residue taken up in alc., the soln. filtered and evapd. in vacuo, and the residue crystd. from dil. alc. pptd. a small amt. of the sulfone, m. 85-6.degree.. The main product was adipic ***acid***. VI (5 g.) stirred 3 hrs. with 20 cc. H₃PO₄, the mixt. heated 3 hrs. at 100.degree. the red soln. poured onto ice and extd. with Et₂O, the washed and dried ext. evapd. and the residue distd. in vacuo

gave 4.0 g. 1,2,3,4-tetrahydrodibenzothiophene (VII), b0.04 110-20.degree.; picrate, m. 106-8.degree.. Oxidation of VII with 30% H2O2 in AcOH and Ac2O produced the corresponding sulfone, m. 175-7.degree., reduced by LiAlH4 in anhyd. Et2O and worked up to give VII. II (2.2 g.) in 0.6 g. AcOH and 0.5 g. Ac2O treated portionwise with 0.46 g. SeO2, the mixt. heated 45 min. on a steam bath, the cooled soln. taken up in H2O and extd. with Et2O, the ext. distd. in vacuo gave dibenzofuran, b0.04 80.degree., and 1.1 g. oil, b0.04 125-30.degree., hydrolyzed by boiling 3 hrs. in 10% NaOH to 4-hydroxy-1,2,3,4-tetrahydrodibenzofuran (VIII) (phenylurethan, m. 143-5.degree.), together with an isomeric alc. (phenylurethan, m. 127-35.degree.). Cyclohexanone (35 g.) in 100 cc. PhMe, 3 g. VIII and 5 g. Al(OCHMe2)3 refluxed 10 hrs., the mixt. steam distd., the residue extd. with Et2O, the washed and dried ext. evapd. and the residue crystd. from Et2O-petr. ether gave 2.2 g. 4-oxo-1,2,3,4-tetrahydrodibenzofuran (IX), m. 63-65.degree.; oxime, m. 182-3.degree. (from 95% alc.); 2,4-dinitrophenylhydrazones, m. 223-5.degree., λ . 394 m. μ . IX (0.5 g.) in 25 cc. CCl4 and 0.450 g. N-bromosuccinimide refluxed 1 hr., the mixt. cooled and filtered, the filtrate evapd. in vacuo at 40.degree., the oily residue refluxed 10 hrs. with 10 cc. PhNMe2, the mixt. extd. with Et2O, the ext. washed with dil. HCl, H2O and 10% NaOH, the alk. ext. acidified and extd. with Et2O, the dried ext. evapd. and the residue recrystd. from petr. ether gave 4-hydroxydibenzofuran, m. 98-9.degree.. II (16 g.) in 20 g. AcOH and 12 g. CrO3 in 28 cc. AcOH stirred 12 hrs. at 25-30.degree., the mixt. decompd. and extd. with C6H6, the ext. washed with satd. aq. Na2CO3 and H2O, dried, evapd. in vacuo and the residue distd. gave 6 g. II and 8 g. 1a,4a-epoxy-1,2,3,4-tetrahydrodibenzofuran (X), b0.05 125-30.degree., m. 108-10.degree.. X (2 g.) refluxed 1 hr. with 10% NaOH, the mixt. extd. with Et2O and the residue acidified yielded o-HOC6H4CO(CH2)4CO2H, m. 91-2.degree.; semicarbazone, m. 182-4.degree.; oxime, m. 125-7.degree.. II (4 g.) added to 2.9 g. BzO2H in 35 cm. CHCl3, after 2 hrs. the mixt. taken up in H2O, the org. layer washed with dil. NaOH and H2O, the dried ext. evapd., and the residue distd. gave a crude product, b0.07 125-30.degree., m. 62-5.degree., ***purified*** by ***chromatography*** in Et2O to 1a,4a-dihydroxy-1,2,3,4-tetrahydrodibenzofuran, m. 70-2.degree.. I (25 g.) and 18 g. BrCH2CO2Et in 200 cc. C6H6-PhMe added portionwise to 9 g. Zn and 2 crystals of iodine in 150 cc. C6H6-PhMe with brief warming to initiate the reaction the mixt. refluxed 3 hrs. with stirring, cooled, and decompd. by addn. of 50 cc. AcOH and 60 cc. MeOH, the clear soln. dild. with H2O, the aq. layer extd. with C6H6, the dried ext. evapd. in vacuo and distd. gave 4 g. I and 30 g. product (XI), b0.01 120-50.degree.. XI (6 g.) refluxed 5 hrs. with 4.5 g. KOH in 25 cc. H2O and 25 cc. alc., the mixt. concd. in vacuo, dild. with H2O and extd. with Et2O, acidified and again extd. with Et2O, the washed and dried Et2O ext. evapd., the clear oily residue taken up in alc., the soln. satd. 15 min. at 0.degree. with dry HCl and kept 12 hrs. at room temp., evapd. in vacuo, the residue taken up in H2O, the soln. extd. with Et2O, the ext. washed with dil. NaOH and H2O, evapd. and the residue distd. gave an oily mixt. of ester and lactone, b0.02 130-40.degree., sapond. by alc. KOH to give 2.4 g. ***acid*** product (XII); S-benzylisothiuronium salt, m. 125-7.degree.; amide, m. 130-2.degree.. Attempts to cyclize XII with concd. H2SO4 or H3PO4-HCO2H gave an ***acid*** [S-benzyl-thiuronium salt, m. 156-8.degree., λ . 273, 279 m. μ . (log ϵ . 2.74, 2.74)], showing no change on cyclization and suggesting isomerization by shift of the double bond. I (5 g.), 2.7 g. NCCH2-CO2Et, 3,6 g. AcOH, and 1.8 g. anhyd. NH4OAc refluxed 18 hrs. in 45 cc. anhyd. C6H6, the cooled mixt. extd. with Et2O, the washed and dried ext. evapd., and the residue distd.

in vacuo gave 5.5 g. distillate, b0.03 130-50.degree., redistd. to yield Et 2-phenoxy-cyclohexylidene-.alpha.-cyanoacetate (XIII), b0.02 130-40.degree.. Hydrolysis of XIII with 10% Na2CO3 caused no change after 7 hrs. refluxing, but hydrolysis by heating 10 hrs. with 20% Na2CO3 in dioxane regenerated I. XIII (2.6 g.) and 4.1 g. NaOH heated 6 hrs. in 30 cc. 95% alc., the reaction products sepd. into ***acid*** and neutral fractions and the neutral fraction ***chromatographed*** over Al2O3 and eluted with 1:1 C6H6-petr. ether gave 1.1 g. trans-2-phenoxy-cyclohexanol (XIV), m. 81-2.degree.; p-toluenesulfonate, m. 116-17.degree.. The infrared spectrum of XIV shows a distinct C-OH band. I (3 g.) in 30 cc. Et2O refluxed 30 min. with 0.4 g. LiAlH4 in Et2O, the mixt. decompd. with excess NH4OH, the Et2O layer washed, dried and evapd., and the residue fractionally recrystd. from Et2O-petr. ether gave cis-2-phenoxy-cyclohexanol (XIVa), m. 80-1.degree., and a small yield of impure XIV. Attempts to condense I with MeNO2 were unsuccessful though the CO group seems particularly reactive to KCN. I (8 g.) in 10 cc. alc. and 16 g. NaHSO3 in 30 cc. H2O heated on a steam bath, the soln. boiled with 2.8 g. KCN and filtered hot, the filtrate kept 17 hrs. at 0.degree. and dild. with H2O, the soln. extd. with Et2O, the washed and dried ext. evapd., the residue (6 g.) crystd. from Et2O-petr. ether, the crude product (m. 100-5.degree.) ***chromatographed*** over Al2O3 and eluted with 3:2 and 4:1 C6H6-petr. ether yielded 20% cyanohydrin (XV), m. 108-11.degree.. Further elution with C6H6 gave 80% cyanohydrin (XVa), m. 78-80.degree.. Dropwise addn. of 25 cc. AcOH to 8 g. I and 16 g. KCN in 80 cc. alc., 4 hrs. ***isolation*** at room temp. and refluxing 1 hr., decompn. with H2O and extn. with Et2O, evapn. of the washed and dried ext., distn. of the residue and crystn. of the distillate from Et2O-petr. ether gave 4.8 g. XVa and 1 g. XV. The presence of the HO group was shown by Zerevitinov detn. and by regeneration of I with NaOMe according to Zemplen or with ammoniacal AgNO3 by the method of Wohl. Attempts to cyclize XV, XVa, and the cyanohydrin from 2-(2-methoxyphenoxy)cyclohexanone failed to give the expected tetrahydrodibenzofuran derivs. XV (1.2 g.) in 60 cc. Et2O added to 0.3 g. LiAlH4 in 30 cc. Et2O at -10.degree., the mixt. refluxed 30 min. and stirred 2 hrs. at room temp., decompd. by addn. of 150 cc. 20% H2SO4, the neutral products extd. with Et2O, the aq. phase made alk. with NH4OH and extd. with CHCl3, the ext. dried over Na2CO3, evapd. in vacuo, and the residue crystd. from Et2O-petr. ether gave 1 g. 1-aminoethyl-2-phenoxy-cyclohexanol, m. 106-8.degree.. Similarly, 1 g. XVa yielded 0.8 g. isomeric 1-aminoethyl-2-phenoxy-cyclohexanol, m. 60-1.5.degree.. A mixt. of XV and XVa (10 g.) in 60 cc. 95% alc. and 20 cc. AcOH was hydrogenated at 46.degree./100 kg. in the presence of 2 g. Raney Ni, the mixt. filtered, the filtrate concd. in vacuo, the residue taken up in H2O and extd. with Et2O, the aq. phase made alk. with Na2CO3 and extd. with CHCl3, and the residue distd. to give 6 g. amine, b0.05 110-18.degree., converted by treatment with 10 g. 98% HCO2H and 20 cc. 30% HCHO 2 hrs. at 100.degree., concg. the cooled mixt. in vacuo, taking up the residue in H2O, making alk. with Na2CO3, extg. with CHCl3, evapg. the ext. and distg. the residue to 1-dimethylaminoethyl-2-phenoxy-cyclohexanol (XVI), b0.02 110-20.degree.; picrate, m. 135-7.degree.; HCl salt, m. 206-8.degree.. Zerevitinov detn. showed the dimethylation to have taken place without dehydration. A mixt. of XV and XVa (5 g.) in 30 cc. 95% alc. hydrogenated at 60.degree./100 kg. in the presence of 1 g. Raney Ni gave 2 g. 1-aminoethyl-2-phenoxy-cyclohexane (picrate, m. 132-4.degree.), dimethylated to 85% 1-dimethylaminoethyl-2-phenoxy-cyclohexane, b0.1 104-6.degree.; picrate, m. 161-3.degree.; HCl salt, m. 171-2.degree.. Conversion of 2-(2-methoxyphenoxy)cyclohexanone by the AcOH method gave

only one isomer of 1-cyano-2-(2-methoxyphenoxy)cyclohexanol, m. 128-30.degree., reduced to 1-aminoethyl-2-(2-methoxyphenoxy)cyclohexanol, m. 73-5.degree.. Various attempts to cyclize XVI failed to produce dibenzofuran derivs. The 2-aryloxycyclohexanones give good yields of Mannich bases resistant to ***acid*** hydrolysis in which the alkylaminoalkyl group is at position 6. These bases have analgesic properties and to press the ***morphine*** structure analogy more closely have been cyclized to tetrahydrodibenzofuran derivs. I (100 g.), 50 g. NHMe₂.HCl, and 25 g. paraformaldehyde in 100 cc. abs. alc. contg. 1 cc. HCl refluxed 3 hrs. and a few min. more after addn. of 100 cc. abs. alc. gave 90 g. pure 6-dimethylaminomethyl-2-phenoxy-cyclohexanone-HCl, m. 177-8.degree.; free base (XVII), m. 78-9.degree.; picrate, m. 143-4.degree.. Similarly were prepd. 6-piperidinomethyl-2-phenoxy-cyclohexanone (XVIIa), m. 82-4.degree. (MeI salt, m. 152-4.degree.), 6-morpholino-methyl-2-phenoxy-cyclohexanone (XVIIb), m. 115-16.degree. (from CHCl₃-Et₂O), and 6-dimethylaminomethyl-2-(2-methoxyphenoxy)cyclohexanone (XVIIc), m. 69-71.degree.; HCl salt, m. 156-8.degree.. XVII (3 g.) in 60 cc. Et₂O added dropwise at 0.degree. to 0.5 g. LiAlH₄ in 60 cc. Et₂O, the mixt. refluxed 2 hrs., decompd. at -10.degree. with 90 cc. 15% KOH, the aq. phase extd. with CHCl₃ and the ext. added to the org. phase, the mixt. washed in a min. of H₂O, dried and evapd. gave cryst. 6-dimethylaminomethyl-2-phenoxy-cyclohexanol (XVIII), m. 95-6.degree.; HCl salt, m. 216-18.degree. (from Et₂O). XVII.HCl (3.2 g.) and 2.2 g. Al(OCHMe₂)₃ in 30 cc. Me₂CHOH refluxed 4 hrs., the mixt. evapd. in vacuo, the residue decompd. by heating with 30 cc. 10N NaOH at 100.degree., the oily residue extd. with CHCl₃, and the washed and dried ext. evapd. yielded an isomeric cryst. amino alc., m. 96-7.degree.. Distn. of the mother liquors produced 1 g. oil, b_{0.02} 120-45.degree. (HCl salt, m. 174-6.degree.), and 0.5 g. XVIII, b_{0.02} 145-50.degree.. Similarly, XVIIc was reduced by LiAlH₄ to 6-dimethylaminomethyl-2-(2-methoxyphenoxy)cyclohexanol, b_{0.03} 150-60.degree.; HCl salt, m. 164-6.degree. (from Et₂O). XVII (4 g.) in 6 cc. HCO₂H and 6 cc. H₃PO₄ at room temp. 20 hrs., heated 3 hrs. at 130.degree., the mixt. poured onto ice and, after preliminary ext. with Et₂O, made strongly alk. with NH₄OH and carefully extd. with CHCl₃, the washed and dried ext. evapd. in vacuo, the residue distd., the distillate taken up in Et₂O, the soln. washed with 10% NaOH and H₂O, dried and distd. in vacuo gave colorless oily 1-dimethylaminomethyl-1,2,3,4-tetrahydrodibenzofuran (XIX), b_{0.05} 87-90.degree.; picrate, m. 156-8.degree.; HCl salt, m. 225-9.degree. (from Et₂O). XIX has .lambda. 254, 280, 287 m.mu. (log .epsilon. 4.06, 3.56, 3.50) in close agreement with II, .lambda. 253, 279, 286 m.mu. (log .epsilon. 4.11, 3.66, 3.65) and in contrast to XVII, .lambda. 272, 278 m.mu. (log .epsilon. 3.18, 3.09). Treatment of the Mannich bases XVII, XVIIa, and XVIIb with PhMgBr and XVII with p-MeOC₆H₄MgBr and working up gave the corresponding substituted cyclohexanols, 1,2,6-Ph(PhO)(R'R''NCH₂)C₆H₈OH (NR'R'' and m.p. given): NMe₂, 98-110.degree. [HCl salt, m. 244-5.degree. (decompn.)]; piperidino, 146-8.degree.; morpholino, 167-9.degree. (HCl salt, m. 98-100.degree.). 2,1,6-PhO(p-MeOC₆H₄)NMe₂CH₂C₆H₈OH b_{0.03} 170.degree., m. 110-13.degree.. VI (6 g.), 3.4 g. morpholine-HCl, and 1.3 g. paraformaldehyde refluxed 20 hrs. in 40 cc. alc., the mixt. treated with 1 g. paraformaldehyde and 0.5 g. concd. HCl and refluxed 3 hrs., and the product worked up gave 2-phenylthio-6-morpholinocyclohexanone (XX), m. 93-5.degree. (picrate, m. 135-7.degree.), stable to 3 hrs. heating at 80.degree. in 10% H₂SO₄. VI (6 g.) and 2.4 g. morpholine treated at 0.degree. by dropwise addn. of 2.5 g. 30% HCHO in 25 cc. MeOH, the mixt. kept 1 hr. at room temp., refluxed 7 hrs. and worked up by the method of Mannich and Strauss (C.A. 38, 14848)

gave a base (XXI), m. 99-102.degree.; picrate, m. 150-2.degree. (decompn.); HCl salt, m. 160-3.degree.. Hydrolysis of XXI with dil. H₂SO₄ gave the original VI and it is suggested that XXI is produced by O-alkylation. A study has been made of the stereoisomerism of the pharmacodynamically important .beta.-aryloxycyclohexylamines prep'd. by the methods of Rericha (C.A. 45, 576b), Hayes and Peterson (C.A. 47, 569a), and Kopp (C.A. 49, 9540i). PhOH (4.7 g.) and 4.8 g. 1,2-cyclo-hexeneimine heated 12 hrs. at 100.degree., the mixt. taken up in Et₂O, the washed and dried ext. evap'd. and the residue dist'd. gave 60% trans-1-amino-2-phenoxy-cyclohexane (XXII), b_{0.06} 117.degree.; picrate, 160-3.degree. (from C₆H₆); HCl salt, m. 213-15.degree. (from Et₂O). XXII (2.5 g.), 1.7 g. EtBr, and 1.5 g. K₂CO₃ in 30 cc. alc. refluxed 12 hrs., the cold mixt. dild. with H₂O, made strongly alk. with NaOH and ext'd. with Et₂O, the ext. refluxed 4 hrs. with EtBr and K₂CO₃, the mixt. reext'd. with Et₂O, the ext. evap'd., and the residue dist'd. gave trans-1-diethylamino-2-phenoxy-cyclohexane (XXIIa), b_{0.05} 120-8.degree.; picrate, m. 112-15.degree. (from alc.). PhONa (from 4.5 g. PhOH and 1.1 g. Na) in 40 cc. abs. alc. and 9 g. cis-2-chloro-1-diethylaminocyclohexane refluxed 6 hrs. and evap'd., the residue in 10% HCl freed from neutral products by Et₂O ext'n. and made alk. with powd. Na₂CO₃, the alk. soln. ext'd. with Et₂O, the washed and dried ext. evap'd. and the residue dist'd. in vacuo yielded 23% XXIIa; perchlorate, m. 122-4.degree. (from Et₂O). XXII (3 g.), 4.5 g. HCO₂H, and 9 g. 30% HCHO heated 2 hrs. at 80.degree. and 1 hr. at 120.degree., the mixt. conc'd. in vacuo and the residue taken up in NaOH, the base ext'd. with CHCl₃, the ext. evap'd. and the residue dist'd. in vacuo gave trans-1-dimethylamino-2-phenoxy-cyclohexane (XXIIb), b_{0.04} 100-5.degree.; picrate, m. 155-7.degree.. PhOH (6.5 g.) treated with 1.6 g. Na in 15 cc. alc. and 50 cc. PhMe and 13 g. cis-2-chloro-1-dimethylaminocyclohexane, refluxed 6 hrs., and the product ***isolated*** as before gave 1 g. XXIIb. I (10 g.), 10 g. HONH₂.HCl, and 10 cc. pyridine in 80 cc. alc. refluxed 12 hrs., the mixt. evap'd. in vacuo, the residue taken up in H₂O, the soln. ext'd. with Et₂O, the washed and dried ext. evap'd., and the residue dist'd. gave 7.8 g. 2-phenoxy-cyclohexanone oxime (XXIII), b_{0.04} 110-35.degree., m. 82.0-4.5.degree.. XXIII (2.5 g.) in 25 cc. Et₂O added dropwise to 0.64 g. LiAlH₄ in Et₂O, the complex refluxed 2 hrs. and decomp'd. at 0.degree. with 100 cc. 30% KOH, the CHCl₃ washings of the aq. phase and the Et₂O layer combined, washed, dried and evap'd., and the residue dist'd. in vacuo yielded 78% cis-1-amino-2-phenoxy-cyclohexane (XXIV), b_{0.02} 110-20.degree.; picrate, m. 173-6.degree. (from alc.); HCl salt, m. 246-8.degree. (decompn.).

XXIII (3.8 g.) in 60 cc. alc. reduced 12 hrs. in the presence of 1 g. Raney Ni, the mixt. filtered and the filtrate, acidified with HCl, conc'd. in vacuo, the residual salt taken up in H₂O and ext'd. with Et₂O, the aq. phase made alk. with NH₄OH and ext'd. with Et₂O, the ext. evap'd. and the residue dist'd. gave XXIV, also obtained by heating 10 g. I and 20 g. HCONH₂ 4 hrs. at 180.degree. in a sealed tube and working up the product or by heating 10 g. I with 20 g. HCONH₂ and 2.4 g. HCO₂H 12 hrs. at 130.degree.. XXIV (5.5 g.), 8.5 g. 98% HCO₂H, and 17.5 g. 30% HCHO heated 2 hrs. at 80.degree. and 2 hrs. at 130.degree., the base ext'd. with dil. HCl to sep. the required tertiary amine from the acetylated secondary base, the ***acid*** phase ***neutralized*** and ext'd. with Et₂O, the ext. washed, dried and evap'd., and the residue dist'd. gave 3 g. pure cis-1-dimethylamino-2-phenoxy-cyclohexane (XXIVa), b_{0.04} 105-8.degree.; picrate, m. 170-3.degree.. XXIVa was similarly prep'd. by the Leuckart-Wallach reaction by heating 10 g. I, 15.2 g. HCONMe₂, and 2.4 g. HCO₂H 16 hrs. at 140.degree.. XXIV (1.6 g.), 3g. EtI in 15 cc. alc., and

0.5 g. KOH in 10 cc. H₂O refluxed 20 hrs., the product taken up in H₂O, the base extd. with Et₂O and distd. gave 1 g. cis-1-ethylamino-2-phenoxy-cyclohexane, b_{0.04} 115-20.degree.; picrate, m. 151-3.degree.. XXIV (9.5 g.) and 25 g. p-MeC₆H₄-SO₃Et in 100 cc. PhNO₂ heated 10 min. at 220.degree., the cold soln. taken up in 20% HCl, the mixt. steam-distd. and the residual liquid filtered, the filtrate made alk. with Na₂CO₃ and extd. with Et₂O, the ext. washed, dried and evapd., the residue distd. and the crude residue, b_{0.05} 100-20.degree., ***purified*** through Ac₂O gave cis-1-diethylamino-2-phenoxy-cyclohexane (XXIVb); picrate, m. 135-7.degree. (from alc.); perchlorate, m. 114-16.degree.. XXIV (5 g.), 3.7 g. EtBr, and 3.5 g. anhyd. K₂CO₃ in 150 cc. abs. alc. refluxed 15 hrs., the mixt. taken up in H₂O and made alk. with Na₂CO₃, extd. with Et₂O, the ext. evapd. and the residue again refluxed 15 hrs. with 3.7 g. EtBr and 3.5 g. K₂CO₃ in 150 cc. alc., the mixt. worked up and the product distd. gave XXIVb, also obtained in 30% yield by heating 5 g. I, 3.8 g. NH₄Et, and 3.2 g. HCHO 12 hrs. at 190.degree.. Lespagnol-Mercier tests on cats showed XVII and XVIIb to have 6% ***morphine*** activity, reduced by reduction of the ketones to alcs. or by introduction of MeO group into the aromatic ring. All activity is suppressed by replacement of the bridge O atom by a CH₂ group.

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TI Aporphine alkaloids. II. The synthesis of 10-oxoaporphines

AU Schlittler, E.; Lindemann, A.

SO Helv. Chim. Acta (1949), 32, 1880-91

DT Journal

LA German

CC 10 (Organic Chemistry)

AB cf. C.A. 42, 7302b. The several reported syntheses of aporphine alkaloids involve Pschorr's ring closure of an aminobenzyltetrahydroquinoline to the phenanthrene deriv. and the resulting yields are generally low (5-20%). Merck and Co. in 1926 claimed that the yield was increased considerably when the "bridge" C atom was CO instead of CH₂. To prove this 2,3,5,6-bis(methylenedioxy)-(I) and 2,3,5,6-tetramethoxy-10-oxoaporphine (II) were synthesized. Piperonal was condensed with hippuric ***acid***, the resulting azlactone hydrolyzed to 3,4-methylenedioxyphenylpyruvic ***acid***, heated with 25% NH₄OH in an autoclave at 100.degree.,

giving

.beta.-(3,4-methylenedioxyphenyl)-N-(4,5-methylenedioxyphenyl)alaninamide, sapond. with NaOH, the corresponding free ***acid***, m. 178-80.degree. (from EtOH-C₆H₆), esterified with CH₂N₂, the Me ester, m. 120-1.degree. (from MeOH) (10 g.), 20 cc. POCl₃, and 50 cc. abs. PhMe refluxed 1 hr., the solvent and excess POCl₃ removed in vacuo, the dark residue washed with petr. ether 50 cc. and Et₂O 50 cc., the last traces of Et₂O removed in vacuo, and the residue heated with 40 cc. water until practically all dissolved and filtered; on standing overnight a cryst. phosphate of Me 1-(4,5-methylenedioxybenzyl)-6,7-methylenedioxy-3,4-dihydro-3-isoquinolinecarboxylate, m. 187-9.degree. (from EtOH), sepd. An aq. soln. of the ester was treated with 20 cc. 30% NaOH, heated 1 hr. on the water bath, cooled, the pptd. Na salt filtered, dried in a vacuum desiccator, then rubbed with 50 cc. 20% AcOH, and the amorphous product filtered and dried to yield 1-(4,5-methylenedioxybenzyl)-6,7-methylenedioxy-3-carboxy-3,4-dihydroisoquinoline (III). This heated dry at 110.degree. until CO₂ evolution ceased (about 10 min.) gave

1-(4,5-methylenedioxybenzyl)-6,7-methylenedioxy-3,4-dihydroisoquinoline, m. 88-9.degree. (from EtOH); picrate, m. 219-21.degree.. III (10 g.) with 1 g. Pd on charcoal in 200 cc. decahydronaphthalene refluxed in a CO₂ atm. 8 hrs. was both decarboxylated and dehydrogenated; the hot soln., filtered, concd. in vacuo to 100 cc. and cooled slowly, yielded 1-(4,5-methylenedioxybenzyl)-6,7-methylenedioxyisoquinoline (IV), m. 168-70.degree. (from C₆H₆) (more could be extd. from the mother liquor); methiodide, m. 268-9.degree. (decompn.) (from Me₂CO). IV (5 g.) was added with stirring over a 30-min. period to 40 cc. concd. HNO₃ at -5.degree., dild. with 250 ml. ice water with constant stirring, the ppt. filtered, washed with water, rubbed with 10 cc. 2 N NH₄OH, and the suspension warmed 10 min. on the water bath, filtered, washed, and dried to yield the (2-nitro-4,5-methylenedioxybenzyl) deriv. (V) of IV, m. 237-8.degree. (from Me₂CO). V (2 g.) in 10 cc. Ac₂O was treated with 3.6 g. finely powd. Na₂Cr₂O₇, carefully heated to boiling, the heat removed as soon as the exothermic reaction set in, the mixt. heated 0.5 hr. longer after the reaction subsided, cooled, dild. with 20 cc. water, made alk. with 30% KOH soln., extd. with CHCl₃, and the ext. dried over K₂CO₃ and concd. in vacuo to give (1-2-nitro-4,5-methylenedioxybenzoyl)-6,7-methylenedioxyisoquinoline (VI), m. 254-5.degree. (from Me₂CO or MeCl). The oxidation could also be accomplished with SeO₂ in dioxane. VI (1 g.) and 8 cc. MeI were heated in a bomb tube at 120.degree. 5 hrs., cooled, filtered, and the crystals rubbed twice with Et₂O and CHCl₃ and dried to give VI.MeI (VII), m. 228-30.degree. (decompn.). VII (400 mg.) in 150 cc. EtOH and 3 drops 20% NaOH soln. was hydrogenated at 21.degree. in the presence of 1 g. Raney Ni catalyst; after 5 mols. of H were absorbed, the catalyst was filtered, the filtrate ***neutralized*** with alc. HCl, the pptd. NaCl filtered, the filtrate concd. in vacuo, the residue dissolved in 15 cc. 2 N HCl, made alk. with 30% KOH, extd. with Et₂O, the Et₂O ext. dried over K₂CO₃, treated with alc. HCl, the solvent removed in vacuo, the residue dissolved in 8 cc. 2 N H₂SO₄ and 4 cc. MeOH, cooled in ice, diazotized with freshly prepd. N NaNO₂ soln., treated with Cu powder 0.4 g. (freed of oil with EtOH), heated on a water bath until evolution of N ceased (about 0.5 hr.), filtered hot, the MeOH removed in vacuo, the H₂SO₄ soln. (VIII) (which should not show coupling ability when tested with R salt in alk. medium) extd. with CHCl₃, the CHCl₃ ext. dried over Na₂SO₄, concd. in vacuo, the residue (110 mg.) hydrogenated in 10 cc. MeOH in the presence of 100 mg. Raney Ni at 17.degree., the catalyst filtered, the filtrate concd. to dryness, the residue taken up in 20 cc. 2 N HCl, made alk. with 30% KOH soln., extd. with 180 cc. Et₂O (the ***purification*** can be repeated), the Et₂O ext. washed with water, dried over K₂CO₃, concd. in vacuo, and the residue treated with HClMeOH to give 50 mg. I.HCl, m. 230-2.degree. (decompn.), (from MeOH). After extg. VIII with CHCl₃ it was made alk. with 30% KOH soln. (IX), extd. with Et₂O (emulsions), the Et₂O ext. taken up in HCl, made alk., and extd. again with Et₂O, dried over K₂CO₃, concd. in vacuo, and the residue converted to the HCl salt as above to yield 10 mg. I.HCl. The alk. soln. IX was ***neutralized*** with HCl, made alk. with Na₂CO₃, extd. with CHCl₃,

and

the CHCl₃ ext. dried over Na₂SO₄ and concd. in vacuo to yield 50 mg. of a base. ***Papaverine*** nitrated as described by Pschorr [Ber. 37, 1926(1904)] gave nitropapaveraldine which was treated with MeI as for VI above, and the resulting 1-(2-nitro-4,5-dimethoxybenzoyl)-6,7-dimethoxyisoquinoline-MeI, m. 217-18.degree. (decompn.), was carried through the subsequent reactions described above, giving II (***purified*** by ***chromatography*** over Al₂O₃), m. 163-8.degree.; HCl salt, m. 211-14.degree.. Heating papaveraldine with

MeI in a bomb tube at 115.degree. gave 1-(4,5-dimethoxybenzoyl)-6,7-dimethoxyisoquinoline-MeI, m. 135-8.degree., which was reduced with 2 mols. H and Raney Ni in EtOH to 1-(4,5-dimethoxybenzoyl)-6,7-dimethoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline, m. 141-2.degree. (from Me2CO-pentane).

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AN 1948:4731 CAPLUS

DN 42:4731

OREF 42:1023d-i,1024a-i,1025a-b

TI The extraction of opium. Twenty-five years of commercial experience in the treatment of opium

AU Barbier, Andre

SO Ann. pharm. franc. (1947), 5, 121-40

DT Journal

LA Unavailable

CC 17 (Pharmaceuticals, Cosmetics, and Perfumes)

AB The 3 standard processes for the extn. of ***morphine*** from opium are described and discussed: (1) the Merck process, dating back to 1830, is obsolete. (2) The Thiboumery and Mohr process, dating back to about 1835, gives low yields because the lime always retains some ***morphine***, and possibly also owing to loss of ***morphine***

by

oxidation in alk. soln. (3) The Robertson-Gregory process (described in Wurtz, Dictionnaire de chimie pure et appliqu. acte. ee 1868; Lebeau et Courtois, Trait. acte. e de pharmacie chimique 2nd ed., Vol. 2, No. 2 (C. A. 32, 3910.4); Schwyzer, Die Fabrikation der Alkaloide (C.A. 22, 1017)) is apparently quite simple in principle, but involves working with very impure, highly viscous solns. and involves difficulties in the washing of the crystals and in the sepn. and ***purification*** of the alkaloids. A process was developed which gave yields of the order of 95% of the ***morphine*** content as detd. by the Harrison method. It consisted essentially in: (1) extn. of the opium with water and pptn. of total alkaloids from the concd. soln. with Na2CO3; (2) extn. of the total alkaloids with an org. solvent (e.g., benzene, toluene, C2HCl3) which removes secondary alkaloids and leaves crude ***morphine*** in the insol. residue; (3) taking up the crude ***morphine*** in water and tartaric ***acid*** and crystn. of ***morphine*** ***acid*** tartrate; (4) taking up the latter salt in water and pptn. of free ***morphine*** with NH4OH. In step (2), lixiviation with benzene removes 6% more of the ***morphine*** than straight extn.; this is attributed to the fact that in lixiviation the benzene which passes out first is satd. with secondary alkaloids, gums, etc., and ***morphine*** is much more sol. in this satd. soln. than in a dil. benzene soln. In the assay of opium for ***morphine***, the delicate points are the trituration of the opium with water (which must be carried out until there is obtained a very smooth and homogeneous paste) and subsequent addn. of and trituration with Ca(OH)2. If these operations are not carried out properly, a hard crust of Ca meconate forms, which prevents complete soln. of the ***morphine***. Water extn. of the opium is effected countercurrently, in 4 stages, the first extn. being carried out at 40-5.degree. and the others at ordinary temp. Before being discarded, the spent opium should be tested for ***morphine***, and if it contains more than 0.3% of the original ***morphine*** content it should be extd. further. The aq. opium ext. is evapd. in vacuo to a vol. of 100 l. per 100 kg. of opium, treated at 85-90.degree. with dry Na2CO3 till decidedly alk. to phenolphthalein, stirred 1 hr. at 85-90.degree. (if no

longer alk., more Na₂CO₃ is added), cooled, filtered, and the ppt. of alkaloids is washed with water. Owing to its water-sol., ***codeine*** should remain in soln., but part of it is found in the total alkaloids, which is attributed to the fact that when the alkaloids are pptd. they at first come down in oily form and dissolve some ***codeine*** which is retained when the oil solidifies on cooling. The drained total alkaloids need not be dried before solvent extn. unless C₂HCl₃ is used as solvent; extn. is continued until the solvent contains less than 1% solids. The crude ***morphine*** is dissolved in a quantity of water at 80-85.degree. equal to twice the wt. of opium used; tartaric

acid is added gradually until the soln. is ***acid*** to litmus (formation of neutral ***morphine*** tartrate); the soln. is treated with decolorizing C, filtered under vacuum, and cooled. An amt. of tartaric ***acid*** equal to that used to ***neutralize*** the crude ***morphine*** is added (soln. ***acid*** to methyl orange) to ppt. ***morphine*** ***acid*** tartrate; after stirring 2 hrs. and standing overnight, the ppt. is filtered under vacuum and washed. Two more crops of crystals can be obtained from the filtrate by concn. They are taken up in water at 85.degree.; NH₄OH is added to faint acidity to methyl red (formation of the neutral tartrate); the soln. is treated with an active decolorizing C (5-10% on the wt. of moist tartrate), preferably also with 0.30% AcONa, 0.20% NH₄ oxalate, and 0.10% Na hydrosulfite. The soln. is filtered; ***morphine*** is pptd. by adding NH₄OH to alky. to phenolphthalein (excess is avoided), filtered under vacuum, washed, and dried at 80.degree.. The product is hydrated, contains about 2% impurities, and is suitable for the manuf. of ***codeine***, dionin, and ***heroin***. A purer ***morphine***, suitable, e.g., for the manuf. of ***morphine*** -HCl, can be obtained by cooling the filtered decolorized soln. of neutral ***morphine*** and NH₄ tartrates, making slightly ***acid*** to methyl orange (HCl is as suitable as, and cheaper than, tartaric ***acid***) to ppt.

morphine ***acid*** tartrate in a high state of purity, which is filtered, washed, and converted into free ***morphine***. It is essential for economic operation to ext. all waters from the alk. pptn. of ***morphine***, as they contain up to 0.75 g. ***morphine*** per l. B. accomplishes this by passing the spent water through a ***column***, countercurrent to BuOH; recovers the BuOH by distn. in the presence of water, and obtains a tarry ***morphine*** residue which is treated with tartaric ***acid*** in the same way as the crude ***morphine***. The secondary alkaloids are obtained as a tarry residue after evapn. of the benzene used to sep. them from the crude ***morphine***. Owing to the ease of prepn. of narceine from narcotine, there is no interest in producing the former from opium. The tarry mixt. is treated with water at 85-90.degree.; tartaric ***acid*** is added to neutrality to methyl red; the mixt. is stirred several hrs. to insure complete soln. of

codeine and thebaine; on cooling, narcotine and

papaverine

crystallize and are filtered out. The filtrate is concd.; tartaric

acid is added to acidity to methyl orange, and the pptd. thebaine

acid tartrate crystals are filtered out, washed, and

purified by recrystn. from water. The free base can be obtained by hot pptn. (preferably from hydroalc. soln.) with NH₄OH or Na₂CO₃.

Codeine is recovered from the thebaine tartrate mother liquor as described further on. The narcotine- ***papaverine*** mixt. is treated in a cohobator with 3 parts boiling Me Et ketone, the soln. is decolorized with C, and cooled to crystallize narcotine, which is filtered out, washed with Me Et ketone, and ***purified*** by recrystn. from alc.

Papaverine is pptd. as the ***acid*** oxalate and
 purified by recrystn. from water. The ***codeine*** is to be
 found in the filtrate from the total alkaloids ppt. and in the mother
 liquors from the thebaine tartrate and from the ***morphine***
 tartrate. These are always treated separately, but all in the same way by
 addn. of NaOH to alk. reaction to phenolphthalein, extn. with benzene,
 distn. of the solvent, taking up with water at 100.degree., and
 purification of the crude ***codeine*** as the HCl salt. The
 extd. alk. waters are acidified to methyl red with Fe-free HCl, heated,
 alkalinized with Na₂CO₃ and cooled; the pptd. impure ***morphine*** is
 filtered out and the filtrate is extd. with BuOH. Synthetic
 codeine is practically always prepd. by decompn. of
 trimethylphenylammonium morphinate, generally by heating in alc. soln.
 under pressure at 140.degree.. B. obtained a good yield by driving off
 the alc. and decompg. the dry salt at 85-8.degree. in vacuo. Brief
 reference is made to the extn. of ***morphine*** from poppy heads and
 poppy straw. Tests were started in 1938, but were interrupted by the war.
 Such extn. may be practical under wartime conditions, but would probably
 be too expensive under ordinary conditions.

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AN 1947:6054 CAPLUS

DN 41:6054

OREF 41:1221h-i,1222a-i,1223a-f

TI Calabash curare alkaloids. I

AU Karrer, P.; Schmid, H.

CS Univ. Zurich, Switz.

SO Helv. Chim. Acta (1946), 29, 1853-70

DT Journal

LA German

CC 10 (Organic Chemistry)

AB This is an orienting study, in which Hoffmann-LaRoche calabash

curare powder and methods of sepn. were used, which, in their
 initial stages, were quite similar to those given by Wieland, Pistor, and
 Bahr (C.A. 35, 5898.2). K. and S. ***isolated*** 4 alkaloids (first
 as the reineckates, and finally as appropriate salts). They were
 C-curarine I (I) (also described by W., P., and B), which is the most
 important alkaloid of calabash- ***curare***, small amts of "alkaloid
 A" (II), and "alkaloid B" (III) and appreciable amts. of calabassine (IV).
 The main steps involved trituration of 200 g. of the calabash powder with
 75 cc. H₂O, followed by extn. on a shaking machine with 1.2 l. MeOH, and
 repeating these extns. (using decreasing amts. of H₂O and MeOH). The
 filtered exts. were evapd. in vacuo at 40.degree., yielding 108.7 g.
 solids, which, in 200 cc. H₂O, were treated with an excess of a satd.
 soln. of reinecke ***acid***. The resulting mixed reineckates (77 g.)
 were extd. with 1.05 l. ***purified*** Me₂CO which dissolved about 55
 g.; this soln. was treated with 5 l. H₂O at 70.degree., the resulting ppt.
 was taken up in 550 cc. Me₂CO and repptd. with 2.75 l. H₂O at 70.degree.,
 and the operation repeated with 400 cc. Me₂CO and 2 l. H₂O, resp. The
 final ppt. of mixed reineckates (V) was 29.8 g. The mother liquors from
 all these ppts. were combined and evapd. to dryness in vacuo at
 35-40.degree., giving a "sol. dried reineckate" fraction of 25.4 g. that
 was not further studied. The tedious, repeated ***chromatographic***
 sepn. of the components of V, using Me₂CO and ***columns*** of
 Brockmann Al₂O₃, are fully described, and are given in a detail that
 cannot be abstracted. A bluish-violet zone in the ***column***, which
 was eluted by means of Me₂CO, and which formed the 1st filtrate of the

initial Al₂O₃ ***column*** used, consisted largely of pure I reineckate (VI) which, together with another fraction of VI, totalled 4.95 g. To VI (combined fractions) in 60 cc. Me₂CO were added 20 cc. H₂O and (dropwise) 153 cc. 7.6% hot aq. Ag₂SO₄. The mother liquors and washings from the resultant ppt. were treated with 33 cc. of a soln. of 0.982 g. BaCl₂·2H₂O. The mother liquors and washings from the resultant BaSO₄ ppt. were combined and evapd. in vacuo, the residue extd. with boiling abs. EtOH, the ext. filtered, evapd., again extd. with abs. alc., evapd., the residue extd. with MeOH, filtered, and the filtrate treated with Et₂O, thus giving 1.832 g. C-curarine I chloride trihydrate (VII), C₂₀H₂₁N₂Cl₃·3H₂O (after repeated crystns. from MeOH-Et₂O or from MeOH-iso-Pr₂O and air drying), or monohydrate (after drying in a high vacuum at 100.degree.). VII gave the following characteristic color reactions: reddish violet with concd. HCl; green with concd. HNO₃; yellowish orange with concd. H₂SO₄; blue with K₂Cr₂O₇ or Ce(SO₄)₂ in aq. ***acid***. The following derivs. of I were prepd. from VII: N-nitrosocurarine I chloride, C₂₀H₂₀N₃Cl₃·3H₂O, giving a green color with H₂SO₄, a yellow color with HCl, no coloration with K₂Cr₂O₇ in aq. H₂SO₄, and a transient pale green with Ce(SO₄)₂; iodide (VIII), C₂₀H₂₁N₂I·H₂O (previously described by Wieland); fluoride (from VII and Ag₂F₂), not analyzed. By heating 144 mg. VII gradually at 300.degree. in a mol. still at 10-4 mm. pressure, a high yield of n-C-curarine I (IX), C₁₉H₁₈N₂, was obtained as an amorphous white powder (from Et₂O). All attempts to obtain cryst. preps. of IX failed and the product was evidently impure in that it contained 80.7-81.2% C instead of 83.16%. However, the analytical data for H and N were good and mol. wt. detns. gave satisfactory results. Besides IX, the mol. distn. yielded very small amts. of a base giving color reactions similar to those of VII but contg. 67.11% C, 6.68% H, and 8.22% N. IX gave the following color reactions: reddish violet with HCl, yellowish orange with H₂SO₄, veering to violet and finally becoming colorless on diln., green with HNO₃, and blue with aq. ***acid*** contg. K₂Cr₂O₇ or Ce(SO₄)₂. IX could not be acetylated with pyridine and Ac₂O and is probably a tertiary amine. Its HCl salt, C₁₉H₁₈N₂·H₂O, does not m. below 300.degree.; picrate (1H₂O), microcrystals from Me₂CO, does not m. below 320.degree.. With MeI, IX yielded a methiodide identical with VIII, which, in Me₂CO and H₂O, was filtered through a Wofatit M ***column*** activated with HCl, thus giving rise to VII in nearly quant. yield. VIII, which gives the typical ***curare*** reactions, was readily converted into the picrate of I, needles (from Me₂CO-H₂O), m. 308-9.degree. (decompn.), which could also be formed directly from VII (prepd. from VI). The formation of a dimeric base (X), C₄₀H₄₂N₄, m. 148.degree. (previously described by Wieland, et al.), resulted from the action of KOH in MeOH on VII. X no longer shows the typical halochromism of VII in acids, and its ultraviolet absorption spectra are different from those of VII. The electrometric titration of the HCl salt of X shows that it is a diacid base (pK 4.95 and 5.76) which is stronger than quinoline, isoquinoline, or tetrahydroquinoline, but somewhat weaker than IX. The various ***chromatographically*** ***purified*** reineckate fractions of IV were combined and converted into the highly insol. picrate (XI) of calebassine, C₂₀H₂₅N₂·C₆H₂O₇N₃, leaflets from Me₂CO, m. 216-18.degree. (decompn.), but m. 186-88.degree. after grinding in an agate mortar. Due to its insoly., XI could not be converted into the chloride by the usual means. However, when XI in Me₂CO was passed through a Wofatit ***column*** activated with HCl, the conversion into calebassinechloride (XII), C₂₀H₂₃N₂Cl₃·3H₂O, needles from MeOHEt₂O (losing 1.5 mols H₂O on drying in vacuo), was nearly quant. HCl and H₂SO₄ give no colorations with XII, but HNO₃ gives a carmine color and ***acid***

solns. of $\text{Ce}(\text{SO}_4)_2$ or $\text{K}_2\text{Cr}_2\text{O}_7$ give reddish-violet colorations. The mother liquors from XII readily yielded XI, thus indicating that the Wofatit treatment had not caused isomerization. From the various combined reineckate fractions of II, alkaloid A chloride, $\text{C}_{20}\text{H}_{21}\text{N}_2\text{Cl} \cdot 3\text{H}_2\text{O}$, needles (from MeOH -iso- Pr_2O), was prepd. in very small amt. It gives a yellow color with HCl , a brownish-red with HNO_3 , no color with H_2SO_4 , a carmine with aq. ***acid*** $\text{K}_2\text{Cr}_2\text{O}_7$, and a reddish-violet with aq.

acid $\text{Ce}(\text{SO}_4)_2$. The corresponding picrate of II m. 269.degree. (decompn). Similarly the reineckate fractions of III gave rise to a chloride, $\text{C}_{20}\text{H}_{25}\text{ON}_2\text{Cl}$ or $\text{C}_{20}\text{H}_{23}\text{ON}_2\text{Cl}$, and a picrate (from Me_2CO - H_2O), m. 193-5.degree.. The chloride of III gives only faint colorations with H_2SO_4 , HNO_3 , and HCl , but deep reddish-violet colorations with aq. $\text{K}_2\text{Cr}_2\text{O}_7$ or $\text{Ce}(\text{SO}_4)_2$. Of the 2 N atoms in I, one is part of a quaternary ammonium salt, whereas the other, due to its possible conversion into a nitroso compd., appears to be a part of a secondary, nonbasic :NH group. The ultraviolet absorption spectra of VII prepd. either from the reineckate of I or from IX are identical and are somewhat similar to those of IX but diverge sharply from those of III, IV, X, and indole.

Neutralization curves of the various bases are shown graphically. Inasmuch as IX has a pK which approaches that of py-tetrahydroisoquinoline HCl and is very different from that of the HCl salts of quinoline, isoquinoline, and py-tetrahydroquinoline, it is believed that I contains a tetrahydroisoquinoline nucleus, or some similar structure in which the N atom is not connected directly with an aromatic nucleus. The limiting toxic doses of salts of the ***curare*** alkaloids ("Grenzdosis") per kg. wt. of frog are 0.1 mg. for I, 0.05-0.07 mg. for II, 0.03-0.05 mg. for III, and 0.2-0.5 mg. for IV. The lethal dose of I for rabbits is 0.03 mg./kg. IV is evidently not identical with Wieland's "C-curarine II," which has a lower toxicity than that of IV.

=> d his

(FILE 'HOME' ENTERED AT 11:15:07 ON 02 NOV 2001)

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31743 FILE DRUGU
119 FILE DRUGUPDATES
273 FILE EMBAL
73230 FILE EMBASE
6227 FILE ESBIODBASE
21 FILE FROSTI
22 FILE FSTA
115 FILE GENBANK
248 FILE HEALSAFE
781 FILE IFIPAT
3680 FILE JICST-EPLUS
7 FILE KOSMET
8111 FILE LIFESCI
16 FILE MEDICONF
53931 FILE MEDLINE
437 FILE NIOSHTIC
617 FILE NTIS
26 FILE OCEAN
15458 FILE PASCAL
247 FILE PHAR
12 FILE PHIC
1316 FILE PHIN
3512 FILE PROMT
35286 FILE SCISEARCH
3 FILE SYNTHLINE
30119 FILE TOXLIT
7020 FILE USPATFULL

2471 FILE WPIDS
2471 FILE WPINDEX
8862 FILE NAPRALERT

L3

QUE ISOQUINOLINE ALKALOID OR CODEINE OR CURARE OR HEROIN OR MOR

SEA L3 (L) (EXTRACT? OR PURIF? OR ISOLAT?)

80 FILE ADISALERTS
19 FILE ADISINSIGHT
19 FILE ADISNEWS
68 FILE AGRICOLA
431 FILE ANABSTR
41 FILE AQUASCI
73 FILE BIOBUSINESS
1 FILE BIOCCommerce
3449 FILE BIOSIS
123 FILE BIOTECHABS
123 FILE BIOTECHDS
442 FILE BIOTECHNO
337 FILE CABA
107 FILE CANCERLIT
5065 FILE CAPLUS
10 FILE CEABA-VTB
16 FILE CEN
48 FILE CIN
38 FILE CONFSCI
5 FILE CROPU
302 FILE DDFB
1570 FILE DDFU
176 FILE DGENE
302 FILE DRUGB
26 FILE DRUGLAUNCH
385 FILE DRUGMONOG2
1 FILE DRUGNL
2888 FILE DRUGU
12 FILE DRUGUPDATES
20 FILE EMBAL
3354 FILE EMBASE
684 FILE ESBIODBASE
2 FILE FROSTI
5 FILE FSTA
10 FILE GENBANK
8 FILE HEALSAFE
66 FILE IFIPAT
198 FILE JICST-EPLUS
674 FILE LIFESCI
3188 FILE MEDLINE
56 FILE NIOSHTIC
49 FILE NTIS
7 FILE OCEAN
873 FILE PASCAL
22 FILE PHAR
111 FILE PHIN
194 FILE PROMT
1700 FILE SCISEARCH
1 FILE SYNTHLINE
2965 FILE TOXLIT

4516 FILE USPATFULL
241 FILE WPIDS
241 FILE WPINDEX
4938 FILE NAPRALERT
L4 QUE L3 (L) (EXTRACT? OR PURIF? OR ISOLAT?)

SEA L4 AND VAT EXTRACT?

SEA L4 AND VAT

1 FILE SCISEARCH
18 FILE USPATFULL
1 FILE WPIDS
1 FILE WPINDEX
L5 QUE L4 AND VAT

FILE 'SCISEARCH' ENTERED AT 11:36:54 ON 02 NOV 2001
L6 1 S L5

INDEX 'ADISALERTS, ADISINSIGHT, ADISNEWS, AGRICOLA, ANABSTR, AQUASCI,
BIOBUSINESS, BIOCOMMERCE, BIOSIS, BIOTECHABS, BIOTECHDS, BIOTECHNO, CABA,
CANCERLIT, CAPLUS, CEABA-VTB, CEN, CIN, CONFSCI, CROPB, CROPU, DDFB,
DDFU, DGENE, DRUGB, DRUGLAUNCH, DRUGMONOG2, ...' ENTERED AT 11:38:17 ON
02 NOV 2001

SEA L4 (L) ACID (L) NEUTRALIZ?

4 FILE ANABSTR
5 FILE BIOSIS
2 FILE BIOTECHNO
24 FILE CAPLUS
5 FILE DRUGU
6 FILE EMBASE
1 FILE ESBIODASE
4 FILE IFIPAT
1 FILE LIFESCI
5 FILE MEDLINE
1 FILE PASCAL
2 FILE PROMT
4 FILE SCISEARCH
1 FILE SYNTHLINE
1 FILE TOXLIT
870 FILE USPATFULL
L7 QUE L4 (L) ACID (L) NEUTRALIZ?

SEA L7 AND (COLUMN? OR CHROMATOG? OR HPLC)

3 FILE ANABSTR
3 FILE BIOSIS
2 FILE BIOTECHNO
9 FILE CAPLUS
1 FILE DRUGU
4 FILE EMBASE
1 FILE LIFESCI
3 FILE MEDLINE
1 FILE PASCAL
3 FILE SCISEARCH

763 FILE USPATFULL
L8 QUE L7 AND (COLUMN? OR CHROMATOG? OR HPLC)

FILE 'CAPLUS, BIOSIS, MEDLINE, SCISEARCH, LIFESCI' ENTERED AT 11:43:28 ON
02 NOV 2001

L9 19 S L8
L10 13 DUP REM L9 (6 DUPLICATES REMOVED)

<-----User Break----->

=>

---Logging off of STN---

=>

Executing the logoff script...

=> LOG Y

COST IN U.S. DOLLARS	SINCE FILE	TOTAL
	ENTRY	SESSION
FULL ESTIMATED COST	68.70	94.14
DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)	SINCE FILE	TOTAL
	ENTRY	SESSION
CA SUBSCRIBER PRICE	-5.29	-5.29

STN INTERNATIONAL LOGOFF AT 11:56:39 ON 02 NOV 2001

Connection closed by remote host

Trying 3106016892...Open

Welcome to STN International! Enter x:x
Welcome to STN International! Enter x:
Welcome to STN International! Enter x:
LOGINID:
LOGINID:sssptal651pxp
PASSWORD:
TERMINAL (ENTER 1, 2, 3, OR ?):2

* * * * * Welcome to STN International * * * * *

NEWS 1 Web Page URLs for STN Seminar Schedule - N. America
NEWS 2 Dec 17 The CA Lexicon available in the CAPLUS and CA files
NEWS 3 Feb 06 Engineering Information Encompass files have new names
NEWS 4 Feb 16 TOXLINE no longer being updated
NEWS 5 Apr 23 Search Derwent WPINDEX by chemical structure
NEWS 6 Apr 23 PRE-1967 REFERENCES NOW SEARCHABLE IN CAPLUS AND CA
NEWS 7 May 07 DGENE Reload
NEWS 8 Jun 20 Published patent applications (A1) are now in USPATFULL
NEWS 9 JUL 13 New SDI alert frequency now available in Derwent's
DWPI and DPCI
NEWS 10 Aug 23 In-process records and more frequent updates now in
MEDLINE
NEWS 11 Aug 23 PAGE IMAGES FOR 1947-1966 RECORDS IN CAPLUS AND CA
NEWS 12 Aug 23 Adis Newsletters (ADISNEWS) now available on STN
NEWS 13 Sep 17 IMSworld Pharmaceutical Company Directory name change
to PHARMASEARCH
NEWS 14 Oct 09 Korean abstracts now included in Derwent World Patents
Index
NEWS 15 Oct 09 Number of Derwent World Patents Index updates increased
NEWS 16 Oct 15 Calculated properties now in the REGISTRY/ZREGISTRY File
NEWS 17 Oct 22 Over 1 million reactions added to CASREACT
NEWS 18 Oct 22 DGENE GETSIM has been improved
NEWS 19 Oct 29 AAASD no longer available

NEWS EXPRESS August 15 CURRENT WINDOWS VERSION IS V6.0c,
CURRENT MACINTOSH VERSION IS V6.0 (ENG) AND V6.0J (JP),
AND CURRENT DISCOVER FILE IS DATED 07 AUGUST 2001
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NEWS PHONE Direct Dial and Telecommunication Network Access to STN
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* * * * * STN Columbus * * * * *

FILE 'HOME' ENTERED AT :11:58 ON 02 NOV 2001

=> index bioscience

FILE 'DRUGMONOG' ACCESS NOT AUTHORIZED
COST IN U.S. DOLLARS

SINCE FILE	TOTAL
ENTRY	SESSION
0.60	0.60

FULL ESTIMATED COST

INDEX 'ADISALERTS, ADISINSIGHT, ADISNEWS, AGRICOLA, ANABSTR, AQUASCI,
BIOBUSINESS, BIOCOMMERCE, BIOSIS, BIOTECHABS, BIOTECHDS, BIOTECHNO,
CABA,
CANCERLIT, CAPLUS, CEABA-VTB, CEN, CIN, CONFSCI, CROPB, CROPU, DDFB,
DDFU, DGENE, DRUGB, DRUGLAUNCH, DRUGMONOG2, ...'
ENTERED AT 14:14:15 ON 02 NOV 2001

59 FILES IN THE FILE LIST IN STNINDEX

Enter SET DETAIL ON to see search term postings or to view
search error messages that display as 0* with SET DETAIL OFF.

=> s walterova.*/au

2	FILE ADISALERTS
0*	FILE ADISINSIGHT
0*	FILE ADISNEWS
11	FILE AGRICOLA
6	FILE ANABSTR
5	FILE BIOBUSINESS
0*	FILE BIOCOMMERCE
36	FILE BIOSIS
2	FILE BIOTECHABS
2	FILE BIOTECHDS
2	FILE BIOTECHNO
8	FILE CABA
4	FILE CANCERLIT
60	FILE CAPLUS
0*	FILE CIN
3	FILE CONFSCI
6	FILE DDFB
18	FILE DDFU
6	FILE DRUGB
0*	FILE DRUGLAUNCH
0*	FILE DRUGMONOG2
0*	FILE DRUGNL
18	FILE DRUGU
0*	FILE DRUGUPDATES
31	FILE EMBASE
3	FILE ESBIODBASE
0*	FILE FOREGE
1	FILE JICST-EPLUS
2	FILE LIFESCI
0*	FILE MEDICONF
30	FILE MEDLINE
47 FILES SEARCHED...	
18	FILE PASCAL
0*	FILE PHAR
0*	FILE PHIC
0*	FILE PHIN
40	FILE SCISEARCH
32	FILE TOXLIT
2	FILE WPIDS
2	FILE WPINDEX

26 FILES HAVE ONE OR MORE ANSWERS, 59 FILES SEARCHED IN STNINDEX

L1 QUE WALTEROVA. ?/A

=> s l1 and isoquinoline?

```
0* FILE ADISINSIGHT
0* FILE ADISNEWS
3 FILE AGRICOLA
1 FILE ANABSTR
2 FILE BIOBUSINESS
0* FILE BIOCOMMERCE
4 FILE BIOSIS
2 FILE BIOTECHABS
2 FILE BIOTECHDS
2 FILE CABA
7 FILE CAPLUS
0* FILE CIN
3 FILE DDFB
3 FILE DDFU
3 FILE DRUGB
0* FILE DRUGLAUNCH
0* FILE DRUGMONOG2
0* FILE DRUGNL
3 FILE DRUGU
0* FILE DRUGUPDATES
3 FILE EMBASE
0* FILE FOREGE
42 FILES SEARCHED...
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3 FILE MEDLINE
1 FILE PASCAL
0* FILE PHAR
0* FILE PHIC
0* FILE PHIN
5 FILE SCISEARCH
6 FILE TOXLIT
```

17 FILES HAVE ONE OR MORE ANSWERS, 59 FILES SEARCHED IN STNINDEX

L2 QUE L1 AND ISOQUINOLINE?

=> s l2 and (purif? or isolat? or extract?)

```
0* FILE ADISINSIGHT
0* FILE ADISNEWS
1 FILE AGRICOLA
1 FILE ANABSTR
2 FILE BIOBUSINESS
0* FILE BIOCOMMERCE
4 FILE BIOSIS
2 FILE BIOTECHABS
2 FILE BIOTECHDS
2 FILE CABA
5 FILE CAPLUS
16 FILES SEARCHED...
0* FILE CIN
1 FILE DDFU
0* FILE DRUGLAUNCH
0* FILE DRUGMONOG2
0* FILE DRUGNL
3 FILE DRUGU
0* FILE DRUGUPDATES
1 FILE EMBASE
34 FILES SEARCHED...
0* FILE FOREGE
0* FILE MEDICONF
47 FILES SEARCHED...
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1 FILE PASO
0* FILE PHAR
0* FILE PHIC
0* FILE PHIN
3 FILE SCISEARCH
4 FILE TOXLIT
58 FILES SEARCHED...

14 FILES HAVE ONE OR MORE ANSWERS, 59 FILES SEARCHED IN STNINDEX

L3 QUE L2 AND (PURIF? OR ISOLAT? OR EXTRACT?)

=> d rank

F1	5	CAPLUS
F2	4	BIOSIS
F3	4	TOXLIT
F4	3	DRUGU
F5	3	SCISEARCH
F6	2	BIOBUSINESS
F7	2	BIOTECHABS
F8	2	BIOTECHDS
F9	2	CABA
F10	1	AGRICOLA
F11	1	ANABSTR
F12	1	DDFU
F13	1	EMBASE
F14	1	PASCAL

=> fil f1, f2, f3, f5, f10

COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	4.05	4.65

FILE 'CAPLUS' ENTERED AT 14:19:36 ON 02 NOV 2001
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FILE 'TOXLIT' ENTERED AT 14:19:36 ON 02 NOV 2001

FILE 'SCISEARCH' ENTERED AT 14:19:36 ON 02 NOV 2001
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FILE 'AGRICOLA' ENTERED AT 14:19:36 ON 02 NOV 2001

=> s l3

L4 17 L3

=> dup rem l4

PROCESSING COMPLETED FOR L4
L5 6 DUP REM L4 (11 DUPLICATES REMOVED)

=> d l5 1- all

YOU HAVE REQUESTED DATA FROM 6 ANSWERS - CONTINUE? Y/(N):y

L5 ANSWER 1 OF 6 CAPLUS COPYRIGHT 2001 ACS DUPLICATE 1

AN 1985:611166 CAPL
 DN 103:211166
 TI **Isolation**, chemistry and biology of alkaloids from plants of
 Papaveraceae. Part XCIX. Separation and quantification of some
 alkaloids
 from Fumaria parviflora by capillary isotachophoresis
 AU Valka, I.; **Walterova, D.**; Popova, M. E.; Preininger, V.;
 Simanek, V.
 CS Med. Fac., Palacky Univ., Olomouc, 775 15, Czech.
 SO Planta Med. (1985), (4), 319-22
 CODEN: PLMEAA; ISSN: 0032-0943
 DT Journal
 LA English
 CC 11-1 (Plant Biochemistry)
 Section cross-reference(s): 9
 AB The isotachophoretic sepn. of some **isoquinoline** alkaloids in
 acid-base partially **purified** exts. from R. parviflora was
 studied. The electrolyte system for model mixts. of alkaloids consisting
 of (-)-stylopine, (-)-canadine, coptisine, berberine, protopine,
 cryptopine, chelidonine, bulbocapnine, papaverine, and parfumine, and for
 the plant exts. contained K⁺ (0.01 M) as the leading ion, CH₃COO⁻ as the
 counter ion, pH 5.5, and H⁺ (acetic acid 0.01 M) as the terminating ion.
 In the plant exts., protopine and parfumine were quant. detd. during F.
 parviflora growth and development from May-June.
 ST alkaloid isotachophoresis Fumaria
 IT Plant growth and development
 (parfumine and protopine changes during, of Fumaria parviflora)
 IT Fumaria parviflora
 (parfumine and protopine of, during development)
 IT Alkaloids, analysis
 RL: ANST (Analytical study)
 (**isoquinoline**, isotachophoretic sepn. of, from Fumaria
 parviflora)
 IT Electrophoresis and Ionophoresis
 (isotachophoresis, capillary, of **isoquinoline** alkaloids)
 IT 130-86-9 28230-70-8
 RL: BIOL (Biological study)
 (of Fumaria parviflora, developmental changes in)

L5 ANSWER 2 OF 6 CAPLUS COPYRIGHT 2001 ACS DUPLICATE 2
 AN 1985:411527 CAPLUS
 DN 103:11527
 TI **Isolation**, chemistry and biology of alkaloids from plants of
 Papaveraceae. Part XCVI. Capillary isotachophoresis of some
isoquinoline alkaloids
 AU **Walterova, Daniela**; Stransky, Zdenek; Preininger, Vladimir;
 Simanek, Vilim
 CS Med. Fac., Univ. Palacky, Olomouc, CS-775 15, Czech.
 SO Electrophoresis (Weinheim, Fed. Repub. Ger.) (1985), 6(3), 128-32
 CODEN: ELCTDN; ISSN: 0173-0835
 DT Journal
 LA English
 CC 64-2 (Pharmaceutical Analysis)
 Section cross-reference(s): 63
 AB The isotachophoretic behavior of quaternary benzo/c/phenanthridine,
 protoberberine and aporphine alkaloids in different electrolyte systems
 is described. The concn. of the leading ion and the pH value of the leading
 electrolyte system is described. The concn. of the leading ion and the
 pH value of the leading electrolyte affect the relative effective mobilities
 of the alkaloids. The system of pH 4.7, contg. the leading K⁺ (0.005 M),
 counter ion acetate, and the terminating ion .beta.-alanine (0.02M) has
 been selected for the quant. detn. of the studied alkaloids in model
 mixts. and plant exts.
 ST capillary isotachophoresis **isoquinoline** alkaloid Papaveraceae

IT Plant analysis
 (isoquinoline alkaloids detn. in medicinal, by capillary isotachophoresis)

IT Chelidonium majus
 Corydalis ophiocarpa
 Papaveraceae
 (isoquinoline alkaloids detn. in, by capillary isotachophoresis)

IT Alkaloids, analysis
 RL: ANT (Analyte); ANST (Analytical study)
 (isoquinoline, detn. of, by capillary isotachophoresis)

IT Electrophoresis and Ionophoresis
 (isotachophoresis, capillary, of isoquinoline alkaloids)

IT 298-45-3 2086-83-1 2141-09-5 2447-54-3 3486-66-6 3621-36-1
 3621-38-3 6872-73-7 7013-69-6 19716-69-9 25651-02-9 34316-15-9
 38691-92-8 55950-32-8 55950-34-0
 RL: ANT (Analyte); ANST (Analytical study)
 (detn. of, by capillary isotachophoresis)

L5 ANSWER 3 OF 6 CAPLUS COPYRIGHT 2001 ACS DUPLICATE 3
 AN 1986:95573 CAPLUS
 DN 104:95573
 TI Isolation, chemistry and biology of alkaloids from plants of Papaveraceae. Part XCV. Practical application of isotachophoresis in analysis of isoquinoline alkaloids
 AU Walterova, D.; Stransky, Z.; Preininger, V.; Simanek, V.
 CS Med. Fac., Univ. Palacky, Olomouc, Czech.
 SO Acta Univ. Palacki. Olomuc., Fac. Med. (1985), 111, 23-36
 CODEN: AUPMAF; ISSN: 0301-2514
 DT Journal
 LA English
 CC 64-2 (Pharmaceutical Analysis)
 Section cross-reference(s): 11

AB Quaternary isoquinoline alkaloids were identified and detd. in model mixts., plant exts., and pharmaceutical preps. by capillary isotachophoresis in a double-capillary system with cond. detection. The isotachophoretic behavior of quaternary benzo[c]phenanthridine, protoberberine [19716-69-9], and aporphine alkaloids in several electrolyte systems as described. The concn. of the leading ion, the pH of the leading electrolyte, and the choice of the terminating electrolyte affect the relative effective mobility values of the alkaloids studied. The pH 4.7 system contg. the leading ion K⁺ (5 .times. 10⁻³ mol/L), counterion acetate, and the terminating ion .beta.-alanine (2 .times. 10⁻² mol/L) was selected for the quant. detn. of sanguinarine [2447-54-3], chelerythrine [34316-15-9], berberine [2086-83-1], and coptisine [3486-66-6] in the above-mentioned samples.

ST plant quaternary isoquinoline alkaloid detn; capillary isotachophoresis alkaloid detn; Papaveraceae isoquinoline alkaloid detn

IT Chelidonium majus
 Corydalis ophiocarpa
 Papaveraceae
 Pharmaceutical analysis
 Plant analysis
 (quaternary isoquinoline alkaloids detn. in, by capillary isotachophoresis)

IT Alkaloids, analysis
 RL: ANT (Analyte); ANST (Analytical study)
 (isoquinoline, detn. of, of Papaveraceae by capillary isotachophoresis)

IT Electrophoresis and Ionophoresis
 (isotachophoresis, capillary, quaternary isoquinoline alkaloids detn. by, in plants and pharmaceutical prepn.)

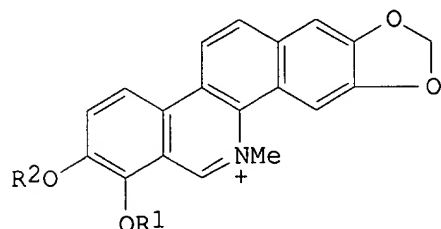
IT 218-38-2D, alkaloids 478-57-9D, alkaloids 2086-83-1 2141-09-5
 2447-54-3 3486-66-6 3621-36-1 3621-38-3 5787-06-4 6872-73-7

7013-69-6 19716-9 25651-02-9 34316-15-9 691-92-8
55950-32-8

55950-34-0

RL: ANT (Analyte); ANST (Analytical study)
(detn. of, in plants and pharmaceutical preps. by capillary isotachophoresis)

L5 ANSWER 4 OF 6 CAPLUS COPYRIGHT 2001 ACS DUPLICATE 4
AN 1985:209507 CAPLUS
DN 102:209507
TI **Isolation**, chemistry and biology of alkaloids from plants of the Papaveraceae. Part LXXXIX. Qualitative and quantitative isotachophoretic analysis of some quaternary **isoquinoline** alkaloids
AU **Walterova, D.**; Preininger, V.; Simanek, V.
CS Med. Fac., Palacky Univ., Olomouc, Czech.
SO Planta Med. (1984), 50(2), 149-51
CODEN: PLMEAA; ISSN: 0032-0943
DT Journal
LA English
CC 64-2 (Pharmaceutical Analysis)
Section cross-reference(s): 9, 31
GI



I, $R^1R^2=CH_2$

II, $R^1=R^2=Me$

AB Sanguinarine (I) [2447-54-3] and chelerythrine (II) [34316-15-9] were detd. in a benzo[c]phenanthridine alkaloid fraction from *Chelidonium majus*

by capillary isotachophoresis. Using the technique a 1 g fraction contained 162.7 mg I and 723.2 mg II. Thus, isotachophoresis was an accurate method suitable for the rapid detn. of quaternary benzo[c]phenanthridine alkaloids used in biol. and clin. assays.

ST benzophenanthridine alkaloid isotachophoresis; *Chelidonium sanguinarine* chelerythrine detn

IT *Chelidonium majus*
(benzophenanthridine alkaloids of, detn. of, by isotachophoresis)

IT Alkaloids, analysis
RL: ANST (Analytical study)
(benzophenanthridine, isotachophoresis of)

IT Electrophoresis and Ionophoresis
(isotachophoresis, of benzophenanthridine alkaloids)

IT 2447-54-3 34316-15-9
RL: ANT (Analyte); ANST (Analytical study)
(detn. of, in *Chelidonium majus* alkaloid fractions by isotachophoresis)

IT 130-86-9 476-32-4 2086-83-1 3486-66-6 24240-04-8
RL: PROC (Process)
(isotachophoresis of)

L5 ANSWER 5 OF 6 AGRICOLA

AN 84:129672 AGRICOLA

DN IND84097963

TI Qualitative and quantitative isotachophoretic analysis of some quaternary

isoquinoline alkaloids [isolated from the aerial parts and roots of *Chelidonium majus*].

AU **Walterova, D.**; Preininger, V.; Simanek, V.
 AV DNAL (450 P697)
 SO *Planta medica* = journal of medicinal plant research., Apr 1984 Vol. 50, No. 2. p. 149-151 ill
 Publisher: Stuttgart, W. Ger. : Hippokrates.
 ISSN: 0032-0943
 NTE Includes references.
 DT Article
 FS Non-U.S. Imprint other than FAO
 LA English
 CC F600 Plant Physiology and Biochemistry
 RN 119-65-3 (ISOQUINOLINE)

L5 ANSWER 6 OF 6 CAPLUS COPYRIGHT 2001 ACS DUPLICATE 5
 AN 1983:516043 CAPLUS
 DN 99:116043
 TI **Isolation, chemistry and biology of alkaloids from plants of the Papaveraceae. Part LXXXVI. Inhibition of acetylcholinesterase activity by some *isoquinoline* alkaloids**
 AU Ulrichova, J.; **Walterova, D.**; Preininger, V.; Slavik, J.; Lenfeld, J.; Cushman, M.; ~~Simanek, V.~~
 CS ~~Med. Fac., Palacky Univ., Olomouc, 775 15, Czech.~~
 SO *Planta Med.* (1983), 48(2), 111-15
 CODEN: PLMEAA; ISSN: 0032-0943
 DT Journal
 LA English
 CC ~~1-12-(Pharmacology)~~
 Section cross-reference(s): 7

AB All 15 quaternary protoberberine and benzophenanthridine alkaloids tested behaved as strong, noncompetitive inhibitors of rat brain acetylcholinesterase [9000-81-1] in vitro; the inhibitory effect of the alkaloids was confirmed in acetylcholine-stimulated rat duodenum and guinea pig ileum tissue preps. The acetylcholinesterase inhibitory activity of the benzophenanthridine alkaloids correlated with their pK_R+ values for pseudobase formation. A study of the effect of surfactants on pseudobase formation of the benzophenanthridine alkaloids suggested a possible effect of the biol. medium on cation-pseudobase equilibration in vivo.

ST acetylcholinesterase inhibition **isoquinoline** alkaloid
 IT Kinetics, enzymic
 (of acetylcholinesterase inhibition by **isoquinoline** alkaloids)
 IT Ionization in liquids
 (of **isoquinoline** alkaloids)
 IT Molecular structure-biological activity relationship
 (acetylcholinesterase-inhibiting, of benzophenanthridine and protoberberine alkaloids)
 IT Alkaloids, biological studies
 RL: BIOL (Biological study)
 (benzophenanthridine, acetylcholinesterase inhibition by)
 IT Alkaloids, biological studies
 RL: BIOL (Biological study)
 (protoberberine, acetylcholinesterase inhibition by)
 IT 2086-83-1 2447-54-3 3486-66-6 6872-73-7 7013-69-6 18203-11-7
 19716-67-7 19716-69-9 33718-28-4 34316-15-9 38691-92-8
 55950-32-8 55950-33-9 55950-34-0 87148-11-6
 RL: BIOL (Biological study)
 (acetylcholinesterase inhibition by)
 IT 9000-81-1
 RL: PROC (Process)
 (inhibition of, by benzophenanthridine and protoberberine alkaloids)

DERWENT-ACC-NO: 1992-156220
DERWENT-WEEK: 199219
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TITLE: New sebum-secretion-promoting agent - contains cycleanine, useful for treating atopic skin inflammation

PATENT-ASSIGNEE: SANZEN PAPER MAKING KK[SANZ]

PRIORITY-DATA: 1990JP-0213268 (August 10, 1990)

PATENT-FAMILY:

PUB-NO	PUB-DATE	LANGUAGE	PAGES	MAIN-IPC
JP 04095014 A	March 27, 1992	N/A	004	N/A

APPLICATION-DATA:

PUB-NO	APPL-DESCRIPTOR	APPL-NO	APPL-DATE
JP04095014A	N/A	1990JP-0213268	August 10, 1990

INT-CL_(IPC): A61K007/00; A61K035/78

ABSTRACTED-PUB-NO: JP04095014A

BASIC-ABSTRACT: Sebum-secretion-promoting agent contains cycleanine.

USE/ADVANTAGE - The agent promotes the secretion function to supply oil to the skin naturally and continuously and impart smoothness and wetness to the skin and hair. It also remedies dry eczema, such as atopic skin inflammation.

In an example, cycleanine is obt'd. by extracting plant alkaloids and purifying or by synthesis. The extraction is done e.g. by extracting the dried prod. of *Stephania cepharantha* Hayata, Menispermaceae, with a mixt. of 0.1N dil. HCl and methanol (1:1), solubilising the extract in aq. HCl, removing the insol., adding chloroform to transfer acidic and neutral substances to the solvent and remove, adding ammonia to make the soln. alkaline and ppte, and leaching out cycleanine with 5-percent-methanol-contg. chloroform by silica gel column chromatogra phy. Agent forms include lotion, oil, ointment, cream and emulsion. The concn. of cycleanine is usually 0.0005-5 wt.%. The agent is usually used by applying to dried parts of the skin 2-4 times a day. In a test on 32 women, the extracts and agent increased the secretion of sebum by 30-40

TITLE-TERMS:

NEW SEBUM SECRETION PROMOTE AGENT CONTAIN CYCLEANINE USEFUL
TREAT ATOPIC SKIN
INFLAMMATION

DERWENT-CLASS: B02 D21

CPI-CODES: B06-E05; B12-A07; B12-D07; B12-L05; D08-B03; D08-B09A;

CHEMICAL-CODES:

Chemical Indexing M2 *01*

Fragmentation Code

D011 D019 D023 D029 E570 H1 H182 H2 H202 H5

H543 H8 M210 M211 M272 M273 M282 M283 M320 M412

M511 M520 M530 M540 M781 M903 M904 P420 P930 P943

Q252 Q262

Ring Index

64958

Specific Compounds

14483U

SECONDARY-ACC-NO:

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